

Diabetic emergencies

Diagnosis and clinical management

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Preface

Diabetes mellitus (DM) comprises a very large chapter, not only of internal medicine but of medicine as a whole. In many countries, the frequency of DM exceeds 10% of the whole population, affecting both genders and all ages. This very common disease not infrequently is accompanied by emergency situations, due both to complications of the disease itself and its treatment. In DM especially, the concept of emergency is potentially tied to the concept of death. For example, a diabetic patient undergoing a moderate-severity operation may have a very bad outcome if his diabetic control during the pre-, peri- and post-operative period is not adequate. The same is true for acute infections and a wide range of other conditions. Acute decompensation of diabetic control can sometimes lead to fatal outcomes in the form of diabetic ketoacidosis or the hyperosmolar hyperglycemic state. Consequently, not only specialists (diabetologists) but also general doctors, internists, surgeons, and other specialty physicians have an obligation to know how to diagnose and deal with such conditions.

For all these reasons it was deemed necessary that this practical book be written for the benefit of both doctors and nurses alike. The writers hope that their by no means easy efforts will be useful in everyday routine practice.

The undersigned expresses his sincere and warmest thanks to all the co-authors of this book, all specialist scientists in this specific field of medicine, for the particular diligence they have shown in dealing with specific chapters.

Many thanks are also expressed to co-author Assistant Professor Konstantinos Makrilakis for his efforts in editing the various chapters of the book and homogenizing them.

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October 2011

CHAPTER 1

Diabetic ketoacidosis in adults

Nikolaos Tentolouris, Nikolaos Katsilambros

Introduction

Diabetic ketoacidosis (DKA) is an acute complication of diabetes mellitus. It is characterized by the triad of hyperglycemia, ketosis, and metabolic acidosis.¹ DKA complicates mainly patients with Type 1 diabetes mellitus, where it may be the first manifestation of the disease, and rarely people with Type 2 diabetes.¹ A special heterogeneous syndrome of “ketosis-prone diabetes (KPD),” in usually adult patients who may lack the typical clinical phenotype of autoimmune Type 1 diabetes, has recently been identified. While initially the condition was thought to be limited to persons of non-Caucasian ethnicity (African-Americans and Hispanics), its prevalence appears to be increasing worldwide.² DKA is an emergency situation and hospitalization of the patient is necessary for immediate treatment. Its frequency is reported as 4.8–8.0 episodes per 1000 diabetic patients.^{3,4} The mortality rate is 2.5–9% and increases along with age, level of consciousness on admission, degree of hyperosmolality and acidosis, as well as severity of azotemia.^{5,6} In the US, hospitalizations due to DKA reach 100,000 and the cost of treatment has been reported as 1 billion dollars per year.⁷

Summary box

- DKA is characterized by the triad of hyperglycemia, ketosis, and acidosis
- DKA complicates mainly Type 1 diabetes

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Definition and classification of DKA in adults

The criteria for the diagnosis of DKA are shown in Table 1.1.^{8,9} DKA can be mild, moderate, or severe. It is considered severe when the arterial blood pH is less than 7.0, the concentration of plasma bicarbonate is less than 10 mEq/L, and the anion gap is greater than

Table 1.1 Diagnostic criteria for diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS)

Diagnostic criteria and classification	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose	>250 mg/dl (>13.9 mmol/L)	>250 mg/dl (>13.9 mmol/L)	>250 mg/dl (>13.9 mmol/L)	>600 mg/dl (>33 mmol/L)
Arterial pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15–18	10–14	<10	>15
Serum ketone*	Positive	Positive	Positive	Small or negative
Urine ketone*	Positive	Positive	Positive	Small or negative
Effective serum osmolality†	Variable	Variable	variable	>320 mOsm/kg
Anion gap (mEq/L)‡	>10	>12	>12	<12
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

*Determination of serum or urine ketone is usually based on a nitroprusside-based reaction.

†Calculation: effective serum osmolality: $2 \times [\text{measured Na}^+(\text{mEq/L})] + \text{glucose (mg/dl)}/18 = \text{mOsm/kg}$ or effective plasma osmolality: $2 \times [\text{measured Na}^+(\text{mmol/L})] + \text{glucose (mmol/L)} = \text{mOsm/kg}$. Normal range = 285–295 mOsm/kg.

‡Calculation: anion gap = $(\text{Na}^+) - [(\text{Cl}^-) + (\text{HCO}_3^-)]$ mEq/L. Normal range = 12 (± 3) mEq/L.

Modified from reference 8 with permission.

12 mEq/L. In severe DKA, the patient is in stupor or in coma. Notably, the severity of DKA does not necessarily coincide with the degree of hyperglycemia.

DKA can rarely be seen without marked hyperglycemia (euglycemic DKA), and in one series of 722 consecutive episodes of DKA only 1.1% had blood glucose levels less than 180 mg/dl (10 mmol/L).¹⁰ Relatively euglycemic DKA has been reported in patients using subcutaneous insulin infusion pumps, which contain short-acting insulin. In these patients, interruption of insulin delivery results in rapid development of ketosis, as patients become insulin deficient within 2–4 hours of cessation of insulin delivery. Euglycemic DKA has also been reported during pregnancy and in subjects using conventional insulin regimens. In these cases, the secretion of large amounts of glucose in the urine or lower rates of hepatic glucose production may account for the relatively “low” glucose concentrations.⁶ Moreover, prolonged fasting before the onset of DKA may result in a lower increase in blood glucose than non-fasting.¹⁰

Since the mid 1990s, increasing attention has been focused on a heterogeneous condition characterized by presentation with DKA in patients who do not necessarily fit the typical characteristics of autoimmune Type 1 diabetes. Earlier reports used the terms “atypical diabetes,” “Flatbush diabetes,” “diabetes type 1B,” and “ketosis-prone type 2 diabetes mellitus” to describe subsets of this condition. It was noted that in some instances patients presented with DKA as the first manifestation of diabetes and subsequently evolved to insulin independence.² This condition, now called “ketosis-prone diabetes (KPD),” comprises a group of atypical diabetes syndromes characterized by severe β -cell dysfunction (manifested by presentation with DKA or unprovoked ketosis) and a variable clinical course. To date, the best attempt to differentiate patients with KPD into clinically distinct subgroups has resulted in the so-called A β classification, based on the presence (A+) or absence (A–) of pancreatic autoantibodies (anti-GAD65 [glutamic acid decarboxylase] and/or anti-IA-2 [islet-antigen autoantibody-2]) and the presence or absence of β -cell functional reserve, as measured by a fasting or glucagon-stimulated C-peptide level.¹¹ Thus, the four subgroups are defined as follows:

- A+ β – autoantibodies present, β -cell function absent
- A+ β + autoantibodies present, β -cell function present
- A– β – autoantibodies absent, β -cell function absent
- A– β + autoantibodies absent, β -cell function present.

A+β− and A−β− patients are immunologically and genetically distinct from each other but share clinical characteristics of Type 1 diabetes, with decreased β-cell function, and both subgroups would be termed Type 1 diabetes (Type 1A and 1B) in the current American Diabetes Association (ADA) classification system. A+β+ and A−β+ patients are immunologically and genetically distinct from each other but share clinical characteristics of Type 2 diabetes, with preserved β-cell functional reserve, and would be termed Type 2 diabetes in the ADA scheme. A−β+ patients comprise the largest KPD subgroup (approximately 50%)¹² and are also the patients who most commonly come to the notice of physicians because they present with DKA yet have the clinical features and subsequent behavior of Type 2 diabetes.¹³ Most A−β+ subjects have new-onset diabetes and are obese, middle-aged males with a strong family history of Type 2 diabetes. In these patients, β-cell function is substantial when measured within 1–2 weeks of the index DKA and improves further when measured after 6–12 months.¹¹

Summary box

- DKA is classified as mild, moderate, or severe
- In severe DKA, altered mental status is the rule
- The degree of DKA does not coincide with the degree of hyperglycemia
- DKA can rarely be seen without marked hyperglycemia
- Ketosis-prone diabetes is a new heterogeneous condition seen in adults presenting with ketoacidosis and having a variable subsequent course

Predisposing factors for DKA

DKA can be the first manifestation of Type 1 diabetes in 10–30% of cases.^{4,5,14} With regard to the remaining cases, DKA is caused by factors associated with either increase in insulin needs (serious infections, trauma or surgery where insulin resistance suddenly and dramatically increases) or decrease of insulin availability (deliberate discontinuation of treatment, dysfunction of infusion systems, inappropriate changes of insulin doses, or mistakes in insulin delivery). In several series, infections were the commonest (28–43%) identifiable cause of DKA followed by errors in insulin delivery or non-

Box 1.1 Precipitating factors of diabetic ketoacidosis

- Infections (mainly lower respiratory tract and urinary tract infections)
- Inappropriate insulin dosage or deliberate omission of insulin therapy
 - non-compliance
 - psychiatric disorders
 - fear of weight gain
 - fear of hypoglycemia
- Cardiovascular disease
- Severe injury
- Hyperthyroidism
- Pregnancy
- Alcohol abuse
- Other co-morbidities (e.g., pancreatitis)
- Drugs
 - corticosteroids
 - pentamidine
 - sympatheticomimetic drugs
 - high dosage of diuretics
 - some antipsychotic drugs

compliance (18–26%).⁹ DKA may be precipitated in patients with Type 2 diabetes during the course of overwhelming infections and less commonly during acute myocardial infarction or trauma.¹⁴ The contributing factors to the development of DKA in patients with known diabetes are depicted in Box 1.1.⁹

Regarding KPD patients, approximately 50% of A-β+ KPD patients have new-onset diabetes and develop DKA without a clinically evident precipitating factor (“unprovoked” A-β+ KPD), while the remainder have long-standing diabetes prior to presentation with DKA, and develop ketoacidosis in association with an acute illness or non-compliance with antidiabetic treatment (“provoked” A-β+ KPD). Unprovoked A-β+ KPD patients display a striking male predominance (2.6:1 male:female) that is quite distinct from provoked A-β+ KPD patients (0.7:1).¹⁵ Unprovoked A-β+ KPD patients show a better prognosis regarding insulin independence compared to the provoked A-β+ KPD group.

Summary box

- DKA is the first manifestation of Type 1 diabetes in 10–30% of cases
- Infections and errors in insulin delivery or non-compliance are the commonest precipitating factors for DKA

Pathogenesis

The combined effect of reduced insulin concentrations (absolute or relative, but always serious) and elevated concentrations of the counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) leads to hyperglycemia, ketosis, dehydration, and electrolyte disturbances.^{6,10} It is of note that, in the absence of insulin deficiency, elevated levels of the counter-regulatory hormones per se do not cause ketosis.⁶ The fundamental difference between DKA and hyperosmolar hyperglycemic state (HHS) is that small residual amounts of insulin in HHS can prevent significant ketosis and, therefore, acidosis. The pathogenesis of DKA and of HHS is depicted in Figure 1.1.

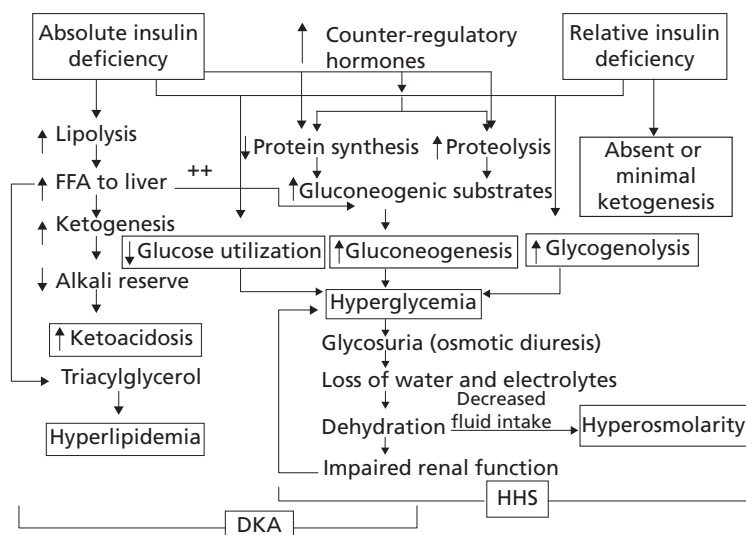


Figure 1.1 Pathogenesis of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). Adapted (with modification) from reference 9 with permission.

Hyperglycemia

Hyperglycemia in DKA is the result of reduced glucose uptake and utilization from the liver, muscle, and fat tissue and increased gluconeogenesis as well as glycogenolysis. The lack of insulin results in an increase in gluconeogenesis, primarily in the liver but also in the kidney, and increased glycogenolysis in liver and muscle.^{8,9} In addition, the inhibitory effect of insulin on glucagon secretion is abolished and plasma glucagon levels increase. The increase of glucagon aggravates hyperglycemia by enhancing gluconeogenesis and glycogenolysis. In parallel, the increased concentrations of the other counter-regulatory hormones enhance further gluconeogenesis. In addition to increased gluconeogenesis, in DKA there is excess production of substances which are used as a substrate for endogenous glucose production. Thus, the amino acids glutamine and alanine increase because of enhanced proteolysis and reduced protein synthesis.^{8,9}

Hyperglycemia-induced osmotic diuresis leads to dehydration, hyperosmolality, electrolyte loss (Na^+ , K^+ , Mg^{2+} , PO_4^{3-} , Cl^- , and Ca^+), and eventually decline in glomerular filtration rate. With decline in renal function, glucosuria diminishes and hyperglycemia worsens. Dehydration results in augmentation of plasma osmolality, which results in water movement out of the cells to the extracellular space. Osmotic diuresis caused by hyperglycemia results in loss of sodium in urine; in addition, the excess of glucagon aggravates hyponatremia because it inhibits reabsorption of sodium in the kidneys. With impaired insulin action and hyperosmolality, utilization of potassium by skeletal muscles is markedly decreased leading to intracellular potassium deficiency. Potassium is also lost due to osmotic diuresis. In addition, metabolic acidosis leads to extracellular movement of potassium in exchange for H^+ , which may be lost in vomit or urine. Moreover, potassium transport is reinforced by protein catabolism due to insulin depletion. Therefore, patients with DKA may present initially with low, normal, or even high serum potassium levels. Nevertheless, a normal serum potassium level in DKA indicates a large body potassium deficit and institution of insulin therapy will lead to future hypokalemia.^{8,9}

The grade of hyperglycemia in DKA varies but rarely exceeds 800 mg/dl (44.4 mmol/L). On the contrary, in HHS, hyperglycemia is usually greater and plasma glucose may exceed 1000 mg/dl (55 mmol/L).⁸

Ketonemia and metabolic acidosis

In DKA, insulin deficiency and increased levels of catabolic hormones (particularly catecholamines) promote breakdown of adipose tissue triglycerides (lipolysis). Concurrently, re-esterification of free fatty acids (FFAs) to triglycerides in adipose tissue is impaired by insulin deficiency. This combination results in the release into the circulation of large quantities of FFAs, which via the portal vein reach the liver. There, in the absence of insulin, FFAs are not converted to triglycerides as normally happens, and they are used, after they have entered the mitochondria, for the production of ketones (or ketone bodies), a procedure facilitated by the elevated glucagon levels.¹⁰ Thus, liver is the site for ketone formation.

The first ketone body produced is acetoacetic acid, which then is reduced to either β -hydroxy-butyrate (β -OHB) or acetone.^{6,9} β -hydroxy-butyrate is the most abundant ketone (75%) to accumulate in blood in DKA. With the exception of acetone, ketone bodies are strong organic acids that dissociate fully at physiological pH, generating equimolar amounts of H^+ and ketoanions. The rapid increase in plasma H^+ concentration outstrips the buffering capacity of the body fluids and tissues and metabolic acidosis develops.^{6,9}

Elimination of ketone bodies (ketolysis) from the body occurs in the mitochondria of organs that can use ketone bodies as an alternative energy source. Skeletal muscle is the main tissue that contributes to ketolysis. Some ketone bodies are eliminated in urine. The anionic charge of ketones leads to excretion of positively charged ions like sodium, potassium, calcium, and magnesium in urine, compounding the loss of water and electrolytes caused by glucosuria. Acetone is excreted via the lungs and produces the characteristic smell of the breath (like nail-varnish remover) in patients with DKA.¹⁰

Summary box

- DKA is due to the combined effect of reduced insulin concentrations and elevated levels of the counter-regulatory hormones
- Reduced glucose uptake and utilization and increased gluconeogenesis as well as increased glycogenolysis result in hyperglycemia

- The combined effects of insulin deficiency and increased levels of the counter-regulatory hormones promote lipolysis; re-esterification of FFAs is inhibited in the absence of insulin
- Large quantities of FFAs enter the circulation and reach the liver where they are metabolized to ketone bodies
- Dissociation of ketone bodies generates H^+ and metabolic acidosis evolves
- Hyperglycemia- and ketonemia-induced osmotic diuresis leads to dehydration, hyperosmolality, and electrolyte loss
- Elimination of ketone bodies occurs mainly in the skeletal muscles

Clinical presentation

The cardinal manifestations of DKA are increasing polydipsia and polyuria, generalized weakness, and altered mental status. In the case of newly diagnosed Type 1 diabetes, variable but rapid weight loss occurs. Symptoms usually develop over several days to weeks.^{1,6,9,10}

Deep and rapid respiration (Kussmaul respiration) is the result of metabolic acidosis. Signs of dehydration and hypovolemia such as hypotension, orthostatic hypotension, tachycardia, poor skin turgor, and dry mucous membranes are often found. Decreased skin turgor suggests 5% dehydration. An orthostatic change in pulse alone suggests a 10% loss of extravascular fluid volume, whereas an orthostatic change in pulse and blood pressure (increase of 15 beats/min and decrease of 10 mmHg) suggests a 15–20% fluid deficit. Supine hypotension indicates either severe dehydration (fluid loss >20%) or underlying sepsis.^{6,10}

Nausea, vomiting, and abdominal pain may be present in DKA. Generalized abdominal pain is more common in young patients with severe acidosis and can mimic a surgical emergency (pseudoperitonitis). Abdominal pain has been associated with acidosis and resolves with treatment. A succussion splash may be evident on examination due to gastric stasis.^{6,10}

Some impairment in mental status is common in DKA, although coma occurs in only 10% of patients. Cerebral edema must always be considered in patients whose consciousness level declines during treatment, although subclinical cerebral edema may be present in DKA before initiation of treatment.^{8,10}

Acidosis induces peripheral vasodilation, which in combination with hypotension may lead to hypothermia and mask infection. In

such cases the rectal temperature should be taken. Obtaining a history and performing an examination to diagnose precipitating causes are important.

Summary box

- Symptoms of DKA include polydipsia, polyuria, malaise, nausea, vomiting, and abdominal pain
- Findings on clinical examination include Kussmaul respiration, signs of dehydration, and altered mental status
- Abdominal pain in severe DKA may mimic a surgical emergency

Laboratory findings

The tests that should be included in the initial laboratory investigation when diabetic ketoacidosis is suspected are shown in Box 1.2.⁶ As shown in Table 1.1, arterial pH is low depending on the severity of acidosis. In severe DKA pH values in the range of 6.7–6.8 have been observed.

DKA is a high anion gap metabolic acidosis. The anion gap is calculated using the formula:

$$(\text{Na}^+) - [(\text{Cl}^-) + (\text{HCO}_3^-)]$$

Box 1.2 Initial laboratory assessment of a patient with suspected diabetic ketoacidosis

- Arterial blood gases
- Serum urea or blood urea nitrogen
- Serum creatinine
- Serum electrolytes (K^+ , Na^+ , Mg^{2+} , P^{3+} , Cl^- , Ca^{2+})
- Complete blood count with differential
- Serum osmolality
- Urinalysis
- Serum or urine ketones
- Blood and urine cultures, when infection is suspected
- Pregnancy test in women of reproductive age
- Electrocardiogram
- HbA_{1c}

The normal value of the gap is 12 (± 3) mEq/L. The anion gap should be corrected by the degree of hypoalbuminemia (add 2.5 mEq/L to the calculated anion gap for every 1.0 g/dl [10 g/L] decrease in serum albumin levels less than 4.5 g/dl [45 g/L]). The severity of acidosis depends on the rate of formation of ketone bodies, the duration for which they have been produced (patients who immediately attend medical treatment have more benign acidosis), and their excretion rate in urine (patients with near normal renal function have the ability to increase H^+ excretion, thereby reducing the severity of acidosis). An anion gap greater than 12 mEq/L suggests anion gap acidosis, while a plasma bicarbonate level greater than 18 mEq/L rules out metabolic acidosis. Arterial PO_2 concentration is increased and PCO_2 is diminished in patients with normal respiratory function as a result of compensatory hyperventilation.^{6,8,10}

Detection of ketone bodies in either serum or urine is usually performed via specific dipsticks that rely on the nitroprusside reaction, which colors the stick purple-violet. It should be noted that these sticks are essentially specific for acetoacetate; they do not react with β -OHB and react only weakly with acetone. During treatment of DKA, 3-OHB is converted to acetoacetate; therefore, nitroprusside-based tests may give the mistaken impression that DKA is either worsening or not resolving. In addition, the test can give false negative results in patients being treated with agents containing sulfhydryl groups (for example captopril) and false positive results if the dipsticks have been exposed to air for a long time.^{6,8,10}

In recent years most biochemical laboratories have measured serum β -OHB directly by spectrophotometry, thus ruling out false results obtained by blood or urine strips. Moreover, some newer glucose meters can measure β -OHB in capillary blood using an electrochemical method with specific strips. The normal level of β -OHB in serum or in capillary blood is <0.5 mmol/L; in DKA values >1.0 mmol/L are usually found. Determination of serum or capillary β -OHB levels has a higher sensitivity and specificity than determination of urine ketone bodies for the diagnosis of DKA.¹⁶ As mentioned above, β -OHB is an early and abundant ketoacid indicative of ketosis. Acetoacetate (determined by the nitroprusside method) may be negative in the blood in early DKA.

DKA is characterized by a significant loss of water and electrolytes. This is a result of osmotic diuresis due to glycosuria as well

Table 1.2 Typical water and electrolyte deficits in diabetic ketoacidosis and hyperosmolar hyperglycemic state

Water	6 L
Sodium	500mmol
Chloride	350mmol
Potassium	300–1000 mmol
Phosphate	50–100 mmol
Calcium	50–100 mmol
Magnesium	25–50 mmol

Adapted (with modification) from reference 6 with permission.

as ketonuria. Despite the contribution of ketonuria, the degree of dehydration in DKA is usually lower than in HHS because the latter arises more gradually and insidiously. Other factors also may contribute to dehydration, such as nausea, vomiting, use of diuretics, and fever.^{6,8,10}

Osmotic diuresis results in electrolyte loss (K^+ , Na^+ , Mg^{2+} , PO_4^{3+} , Cl^- , Ca^+). The average deficit of water and electrolytes in DKA is shown in Table 1.2. As mentioned above, serum potassium levels are usually normal, but they may be low or even elevated.

The initial serum sodium concentrations are usually low because of water movement from the intracellular to the extracellular compartment in an attempt to compensate for hyperosmolality. In patients with high plasma osmolality, and therefore greater osmotic diuresis, with inadequate fluid compensation, serum sodium can be increased. However, this is usually observed in HHS and less often in DKA. Serum sodium levels should be corrected for hyperglycemia; for each 100mg/dl glucose >100mg/dl (5.6 mmol/L), add 1.6mEq to measured sodium value to obtain a corrected serum sodium value.^{6,8,10}

Phosphorus levels in plasma are usually normal or increased. However, as in the case with potassium, the total body phosphorus deficit is large as a result of shift from the intracellular to the extracellular compartment and loss in urine.¹⁰

Most patients with DKA have leukocytosis with a left shift. This is due to dehydration and stress response to ketonemia and hyper-

glycemia and does not necessarily suggest infection. However, a white cell count $>25,000/\mu\text{l}$ warrants a comprehensive search for infection. Increased hematocrit levels are found in most cases of DKA as a result of dehydration.⁸

Effective serum osmolality can be measured directly in the laboratory or derived from the following formula:

$$2 \times [\text{measured Na}^+ (\text{mEq/L})] + \text{glucose (mg/dl)} / 18 = \text{mOsm/kg}$$

$$\text{or } 2 \times [\text{measured Na}^+ (\text{mEq/L or mmol/L})] + \text{glucose (mmol/L)} = \text{mOsm/kg}$$

The normal range is 285–295 mOsm/kg. The level of consciousness correlates more closely with serum osmolality than with pH. Values $>340 \text{ mOsm/kg}$ suggest great fluid loss and are associated with altered consciousness level (stupor or coma). However, such high levels are not usual in DKA and are more often seen in HHS. On the other hand, serum osmolality levels $<320 \text{ mOsm/kg}$ warrant further evaluation for coma from causes other than DKA.^{9,14}

Serum amylase and lipase levels may be increased in 16% and 25% of cases, respectively, in DKA in the absence of acute pancreatitis.^{17,18} The cause of this elevation is not known. Although serum lipase measurement is more specific for the diagnosis of pancreatitis, this is not true in DKA, and elevations of either amylase or lipase to more than three times normal do not confirm the diagnosis of pancreatitis in this situation. However, it should be noted that coexisting acute pancreatitis may be present in 10–15% of patients with DKA. Serum creatinine may be falsely elevated because of acetoacetate interference with the colorimetric creatinine assay.¹⁰

Determination of HbA_{1c} is indicative of the degree of diabetes control in the previous 2–3 months.

Summary box

- DKA is a high anion gap metabolic acidosis
- Ketone bodies can be detected in serum and urine
- Although serum electrolyte levels may be normal, the total body deficit is large
- Serum osmolality is increased
- White blood cell count and hematocrit are increased
- Serum amylase and lipase levels may be increased in the absence of acute pancreatitis

Differential diagnosis

Other causes of ketoacidosis need to be considered when patients with diabetes present with ketosis. These include starvation ketosis and alcoholic ketoacidosis.

Starvation ketosis evolves when a person consumes a small amount of food (<500Kcal) for many days. However, starvation ketosis usually does not cause acidosis, blood glucose levels and osmolality are normal, and serum or urine ketones are only slightly elevated.^{6,9}

Pregnant women are more prone to develop ketoacidosis (pregnancy ketosis) due to starvation. This happens because pregnancy is associated with accelerated lipolysis and ketogenesis and starts within 6 hours of fasting.⁶ For this reason, in women of reproductive age, clinicians should consider screening for pregnancy, which has been associated with the onset of DKA.¹⁹

Alcoholic patients may develop ketoacidosis (alcoholic ketoacidosis) after heavy drinking. Alcoholic ketoacidosis is characterized by normal or even relatively low serum glucose levels and osmolality, low pH, increased anion gap metabolic acidosis, and increased β -OHB concentration levels. For this reason, the results of nitroprusside-based tests for the assessment of ketosis may be normal or slightly positive.^{6,8}

In case of doubt, other causes of high anion gap metabolic acidosis should be considered in the differential diagnosis (lactic acidosis: measurement of plasma lactate; salicylate intoxication: salicylic acid level measurement; methanol or ethylene glycol ingestion: determination of methanol or ethylene glycol; uremic acidosis: determination of urea and creatinine).

Summary box

- Differential diagnosis of DKA includes starvation ketosis and alcoholic ketoacidosis
- In starvation ketosis, blood glucose and pH are normal, while ketones are slightly increased
- Alcoholic ketoacidosis is characterized by normal blood glucose levels and osmolality, low pH and high anion gap metabolic acidosis, as well as high β -OHB levels
- In case of doubt, other causes of high anion gap metabolic acidosis should be considered

Clinical management

Treatment consists of rehydration with intravenous fluids, the administration of insulin, and replacement of electrolytes. General medical care and close supervision by trained medical and nursing staff is of paramount importance in the management of patients with DKA. A treatment flowchart (Table 1.3) should be used and updated meticulously. A urine catheter is necessary if the patient is in coma or if no urine is passed in the first 4 hours.

Replacement of water deficit

Patients with DKA have severe dehydration. The amount of fluid needing to be administered depends on the degree of dehydration (Table 1.4). Fluid replacement aims at correction of the volume deficit and not to restore serum osmolality to normal. Isotonic solution NaCl (0.9%) (normal saline; osmolality 308 mOsm/kg) should be administered even in patients with high serum osmolality since this solution is hypotonic compared to the extracellular fluid of the patient.¹⁰

The initial rate of fluid administration depends on the degree of volume depletion and underlying cardiac and renal function. In a young adult with normal cardiac and/or renal function 1 L of normal saline is administered intravenously within the first half- to one hour. In the second hour administer another 1 L, and between the third and the fifth hours administer 0.5–1 L per hour. Thus, the total volume in the first 5 hours should be 3.5–5 L [1]. If the patient is in shock or blood pressure does not respond to normal saline infusion, colloid solutions together with normal saline may be used.^{1,6}

Some authors suggest replacement of normal saline with hypotonic (0.45%) saline solution after stabilization of the hemodynamic status of the patient and when corrected serum sodium levels are normal.⁸ However, this approach may result in rapid movement of extracellular water into cells as blood glucose and osmolality fall with treatment; such shifts have been implicated in the pathogenesis of cerebral edema.^{6,10} Hypotonic saline solution can be used when serum osmolality is very high; this is rare in DKA but common in HHS.

When the blood glucose level falls below 250 mg/dl (13.9 mmol/L), or according to other authors 200 mg/dl (11.1 mmol/L), normal saline should be discontinued and replaced immediately by dextrose 5% solution at a rate of 250 ml per hour. Alternatively infusion of

Table 1.3 Suggested flowchart for the monitoring of treatment of diabetic ketoacidosis and hyperosmolar hyperglycemic state

Date Time	Mental status	Blood pressure	Pulse	Glucose	Na	K	Cl	HCO ₃	Ca	PO ₄	pH	PaO ₂ / PCO ₂	Ketones in blood	IV fluids	Insulin dose IU/h	Urine output

Adapted (with modification) from reference 6 with permission.

Table 1.4 Suggested fluid replacement in patients with diabetic ketoacidosis. Use isotonic NaCl 0.9% solution in the first 4 hours to maintain hemodynamic status. Change to 5% dextrose solution when blood glucose is ≤ 250 mg/dl (13.9 mmol/L)

Hours	Volume
1 st half-hour to 1 hour	1 L
2 nd hour	1 L
3 rd hour	500 ml–1 L
4 th hour	500 ml–1 L
Total 1 st –5 th hours	3.5–5 L
6 th –12 th hours	250–500 ml/h

Adjust the type and rate of fluid administration in the elderly and in patients with congestive or renal heart failure.

Adapted from reference 6 with permission.

a mixture of 5% dextrose with 0.45% NaCl, instead of dextrose 5%, can be used.⁹ Glucose infusion together with insulin administration suppresses lipolysis and ketogenesis and maintains blood glucose levels at near normal (120–180 mg/dl [6.6–10 mmol/L]) levels. Intravenous glucose is given without interruption until the patient is eating again and subcutaneous insulin resumed.^{1,6,8,10}

In total, 6–12 L of fluid may be required in the first 24 hours for the correction of dehydration.⁶ The duration of intravenous fluid administration is on average 48 hours. Restoration of water deficit requires special attention not only to the ongoing loss of fluid in the urine because hyperglycemia continues for several hours after starting treatment but also to avoid overhydration, particularly in patients with impaired cardiac or renal function. Urine output monitoring is very important for such patients.

Intravenous soluble insulin infusion

Administration of insulin is the etiologic treatment of DKA because it reduces blood glucose levels by inhibiting hepatic glucose production, increasing glucose uptake and utilization in peripheral tissues and inhibiting lipolysis and ketogenesis. Insulin administration must begin in parallel with fluid replacement therapy.

As recently as the early 1970s, large doses of insulin were administered for the treatment of DKA. Then several randomized trials showed that the administration of small doses of insulin is effective in the resolution of DKA and reduces the risk of hypoglycemia and hypokalemia.^{20,21} Nowadays, according to most protocols,^{1,6,8} the administration of an initial intravenous bolus of soluble rapid-acting insulin is recommended. Some suggest a bolus administration of insulin (usually 0.1 IU/kg) followed by infusion of 0.1 IU/kg per hour (usually 5–7 IU per hour). Others suggest infusion of insulin at a higher dose (0.14 IU/kg per hour) without an initial bolus administration. The infusion solution is usually prepared by adding 100 IU of insulin to 250 ml normal saline and is administered with special infusion pumps. If such pumps are not available, 50 IU of rapid-acting soluble insulin can be diluted in 500 ml normal saline, thus creating a solution with a concentration of 1 IU of insulin for every 10 ml solution, and then infusing at the desired rate (for example 50–70 ml/h if 5–7 IU per hour are needed) in parallel with the normal saline administered for the correction of dehydration using a Y connector or preferably via a separate venous line. The addition of albumin to the solution to discourage insulin absorption to the walls of the infusion device is not necessary.²²

Other routes of insulin administration

Instead of continuous infusion, insulin can be administered subcutaneously or intramuscularly with equally good results, providing that the patient is hemodynamically stable. Intermittent intramuscular soluble insulin administration in the deltoid muscle (5 IU) every 2 hours after an initial loading dose of 20 IU is acceptable for the treatment of uncomplicated DKA.

If subcutaneous insulin is to be used, patients typically receive an initial dose of 0.2 IU/kg (for example 16 IU in an 80 kg person) followed by 0.1 IU/kg every hour (for example 8 IU for an 80 kg person) or an initial dose of 0.3 IU/kg and subsequently 0.2 IU/kg every 2 hours while blood glucose remains above 250 mg/dl (13.9 mmol/L). When glucose levels fall to below 250 mg/dl (13.9 mmol/L) the insulin dose may be decreased by half and administered every 1 or 2 hours until resolution of DKA. Subcutaneous or intramuscular insulin is indicated for the management of DKA in centers where it is difficult to monitor low-dose intravenous infusions and may be associated with a lower cost of hospitalization by avoiding intensive care unit placement.¹⁹ Milder

forms of DKA can also be treated safely with subcutaneous or intramuscular insulin. Comparison of subcutaneous, intramuscular, and intravenous regimens for treatment of DKA has shown no significant difference in outcomes, except for a more rapid decline in glucose and ketones in the first 2 hours with the intravenous infusion.^{22,23}

Recently, treatment with subcutaneous rapid-acting insulin analogs (lispro or aspart every 1 or 2 hours in non-intensive care unit settings) was shown to be an effective alternative to the use of intravenous regular insulin in the treatment of DKA.^{24,25} The rate of decline of blood glucose concentration and the mean duration of treatment until correction of ketoacidosis were similar among patients treated with subcutaneous insulin analogs every 1 or 2 hours or with the intravenous regular insulin. An initial intramuscular or subcutaneous dose of 0.3 IU/kg (for example, 24 IU in an 80 kg person), followed by 0.1 IU/kg every hour (for example, 8 IU every hour in an 80 kg person), can be used. However, it is recommended that until more data on efficacy are available, patients with severe DKA, hypotension, edema, or associated severe critical illness are managed with intravenous soluble insulin.⁹

Some doctors prefer the repetitive-bolus intravenous administration of insulin: specifically the administration of 20–50 IU every 2 hours is recommended.¹⁰ When glucose levels fall below 250 mg/dl (13.9 mmol/L), the treatment changes to subcutaneous administration every 4–6 hours. However, because intravenous insulin has a plasma half-life of about 8–9 minutes, intermittent intravenous administration may lead to unpredictable and fluctuating insulin concentrations. In addition, high insulin doses may lead to hypokalemia and late hypoglycemia.

It should be noted that the protocols of fluid administration may vary depending on the clinic, but their basic principles and therapeutic goals remain the same. Insulin administration should produce a steady and predictable fall in blood glucose levels averaging 50–70 mg/dl per hour (2.8–3.9 mmol/L per hour). If blood glucose does not fall by at least 10% in the first hour (or less than 50 mg/dl [2.8 mmol/L per hour]) on the insulin infusion rate, the insulin dose should be doubled or increased by 0.05–0.1 IU/kg every 1–2 hours (or 1–2 IU every 1–2 hours), providing that other causes for lack of response have been excluded. These include worsening of acidosis or inadequate hydration.⁶ When blood glucose is below 250 mg/dl (13.9 mmol/L) and/or there is improvement in

clinical status with decrease in blood glucose greater than 75 mg/dl (4.2 mmol/L), the rate of insulin infusion should be decreased by 0.05–0.1 IU/kg per hour (or 1–2 IU per hour). In any case, the rate of insulin infusion should not be less than 1 IU per hour. If blood glucose has fallen to below 80 mg/dl (4.5 mmol/L), insulin infusion should be discontinued for no more than 1 hour and restarted at a lower infusion rate. During insulin infusion after the first few hours the blood glucose levels should be maintained between 140 and 180 mg/dl (7.8–10 mmol/L).^{1,6,10}

The intravenous infusion of insulin can be stopped when DKA has been corrected (blood glucose is less than 200 mg/dl [11 mmol/L], HCO_3^- is above 18 mEq/L, pH is higher than 7.3, and anion gap is normal). Then, feeding and per os hydration as well as subcutaneous administration of insulin can be initiated.⁸

Patients are given soluble insulin or rapid-acting insulin analogs 1–2 hours before discontinuation of intravenous insulin to allow sufficient time for the injected insulin to start to work and before each meal. In parallel, injection of intermediate- or long-acting insulin should be initiated to provide the basal insulin requirement. It is not recommended that patients in transition from intravenous to subcutaneous insulin only are placed on short-acting insulin using sliding scales. If patients used insulin before admission, the same dose can be restarted in the hospital. Newly diagnosed patients with Type 1 diabetes require a total daily dose of 0.5–0.8 IU/kg, divided as 30–50% basal insulin and the remainder as rapid-acting insulin before each meal. Fingerstick glucose measurements before meals and at night should be done to correct for possible fluctuations in insulin needs.^{8,10}

In patients with KPD, long-term management can be guided rationally by accurate classification based upon assessment of β -cell functional reserve, β -cell autoantibodies, and in some instances, HLA allelotyping. Although assessment of these parameters in all patients presenting with DKA is ideal, cost constraints and assay availability may make it prohibitive in some regions.

At presentation the type of diabetes is unknown and it is advisable that all patients continue subcutaneous insulin administration on discharge from the hospital until further testing (β -cell functional reserve and pancreatic autoantibodies) is performed. Assessment of β -cell secretory reserve and β -cell autoimmunity can be performed 1–3 weeks after resolution of ketoacidosis, to minimize the acute effects of glucose toxicity or desensitization on

β -cell function. β -Cell secretory reserve (as measured by fasting plasma C-peptide, C-peptide response to glucagon stimulation, and C-peptide to glucose ratio) following DKA resolution is the strongest predictor of long-term glycemic control and insulin dependence.²⁶ Patients are classified as " β -" if the fasting serum C-peptide concentration is less than 1 ng/ml (0.33 nmol/L) and the peak serum C-peptide response to glucagon (measured at 5 and 10 minutes after intravenous injection of 1 mg glucagon) is less than 1.5 ng/ml (0.5 nmol/L).¹¹ Although these cut-off points do not independently predict the potential for successful and safe withdrawal of insulin, a high ratio (>11) of fasting C-peptide (in nmol/L) to glucose (in mmol/L) at 6 months predicts such a course among β + patients.²⁶

Patients with poor β -cell function (β -) after resolution of the DKA event typically require long-term exogenous insulin therapy, regardless of autoantibody status. Patients with β -cell secretory reserve who are antibody negative ($A-\beta+$) are often able to discontinue insulin, especially if they had unprovoked DKA as the initial manifestation of diabetes. The duration of the process of insulin withdrawal is variable and may range from 10 to 14 weeks to longer. If, after discontinuation of insulin, blood glucose values increase without development of ketosis, treatment with oral or injectable agents to lower blood glucose is required. If the patient develops ketosis upon decreasing the insulin dose, insulin should be intensified. In this setting, attempting to withdraw insulin a second time is not suggested. Patients with preserved β -cell function who have autoantibodies ($A+\beta+$) have a variable course, with some demonstrating progressive β -cell deterioration and others long-term preservation. This group of individuals requires more careful monitoring, and these patients may benefit from HLA genotyping to provide additional prognostic markers of clinical behavior.

Ketonemia and ketonuria may continue for up to 36 hours because of the slow elimination of ketone bodies.⁶ When ketonemia is used to assess response to therapy, determination of β -OHB in blood is recommended.

Treatment of acidosis

Most experts do not recommend the administration of bicarbonate because acidosis is corrected with insulin infusion and rehydration. The administration of bicarbonate in severe acidosis (pH less than

7.0) remains controversial.⁸ Severe metabolic acidosis exerts a negative inotropic effect on the heart, induces vasodilation and hypotension, reduces glucose uptake and utilization, and promotes ventricular arrhythmias.⁶ On the other hand, bicarbonate therapy may lead to worsening of hypokalemia (especially at the beginning of bicarbonate administration), intracellular acidosis in the central nervous system (paradoxical acidosis),²⁷ and metabolic alkalosis.⁶ One study showed that bicarbonate administration had no benefits for patients with DKA and initial pH 6.9–7.15.²⁸ However, in this trial the number of patients with pH in this range was very small. Based on existing evidence and expert opinion, it may be prudent to administer 50 mmol of bicarbonate in 200 ml water with 10 mEq of potassium chloride over 1 hour in patients whose pH is 6.9–7.0 or serum bicarbonate less than 5 mEq/L. In patients with pH less than 6.9, doubling of the above bicarbonate dose is recommended. Arterial pH should be monitored 2 hours later and the dose should be repeated if pH remains lower than 7.0.^{8,10}

Electrolyte replacement

Replacement of sodium and chloride deficits is achieved by the administration of normal saline as described above. Particular attention should be paid to potassium restoration. As mentioned, serum potassium concentrations are usually normal or increased despite the significant total body deficit. During treatment of DKA potassium levels are decreased, sometimes very quickly, because correction of acidosis and the insulin infusion move potassium into the intracellular compartment. Hypokalemia may cause severe arrhythmias and cardiac arrest. If potassium levels are less than 3.3 mEq/L at any point during therapy, insulin should be stopped and potassium should be administered.^{6,10}

Potassium replacement must be performed as follows:⁹

- Low potassium (less than 3.3 mEq/L): insulin should be immediately discontinued; give 20–30 mEq of potassium per hour until potassium levels exceed 3.3 mEq/L; then resume insulin infusion.
- Potassium levels between 3.3 and 5.3 mEq/L: add 20–30 mEq of potassium in each liter of intravenously administered fluid to keep serum potassium between 4 and 5 mEq/L.
- Potassium levels above 5.3 mEq/L: potassium is not administered until levels reach the normal value. Repeat potassium measurement in 2 hours.

Potassium is replaced as KCl. Some authors recommend replacement of one third of the potassium with KPO_4 to avoid excessive chloride administration and to prevent hypophosphatemia.⁶ Special attention is needed in patients with impaired renal function or anuria to avoid hyperkalemia.

It should be noted that the goal of treatment is not immediate restoration of the total potassium deficit. This can be done progressively and completed with feeding.

Phosphate depletion is common in DKA, and serum phosphate levels may decline during treatment with insulin because phosphate is taken up intracellularly. However, phosphate replacement should be reserved only for patients with severe hypophosphatemia (serum levels $<1.5 \text{ mg/dl}$ [0.48 mmol/L]) providing that serum calcium levels are normal.⁸ Oral phosphate repletion is always preferable to intravenous repletion and should be commenced as soon as patients are able to take food by mouth.⁹ The management of DKA is depicted in Figure 1.2.

Summary box

- Treatment of DKA includes rehydration, insulin administration, and correction of electrolyte deficit
- Administer 3.5–5L of normal saline in the first 5 hours and 6–12L in the first 24 hours
- The average duration of fluid administration is 48 hours
- Intravenous infusion of insulin is preferable to intramuscular or subcutaneous injection
- Pay particular attention to the correction of hypokalemia
- Once the patient can eat, discontinue intravenous insulin and start subcutaneous intermediate- or long-acting insulin together with preprandial rapid-acting insulin
- Correction of metabolic acidosis may be indicated when arterial pH is less than 7.0

Patient monitoring

The protocol in Table 1.5 is suggested for the monitoring of patients with DKA and should be meticulously completed (see Table 1.3) (it may vary between clinics).¹

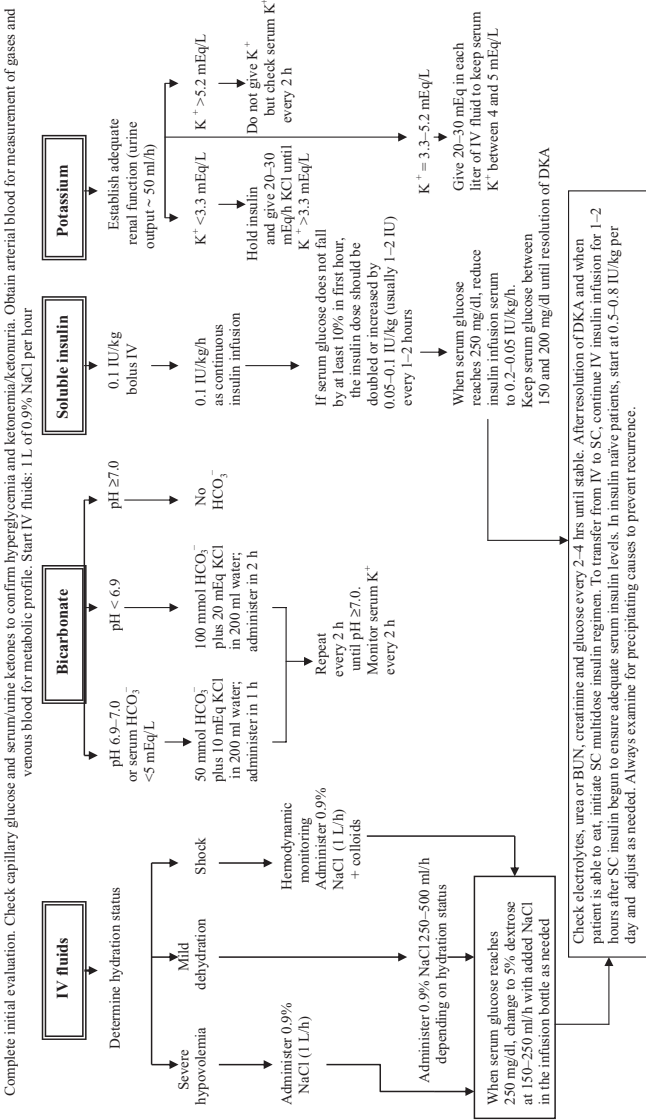


Figure 1.2 Proposed algorithm for the treatment of diabetic ketoacidosis (Modified from Reference 9).

Table 1.5 Suggested protocol for monitoring patients with diabetic ketoacidosis

Assessment	Time interval
Clinical	
Vital signs (blood pressure, diuresis, breathing, pulse)	20–30 min
Mental status (if the patient is in a coma)	20–30 min
Biochemical	
Blood glucose	1 hour
Na, K, pH, anion gap	0, 2, 6, 10, 24 hours
HCO ₃ ⁻ , PaO ₂ , O ₂ sat, PCO ₂ , osmolality	2–4 hours
Serum urea	0, 12, 24 hours
Urinary ketones	0, 4, 8, 12, 18, 24 hours
Serum ketones	0, 6, 12, 24 hours

Complications

Complications of DKA include hypoglycemia (due to over-treatment), hypokalemia, cerebral edema, non-anion gap hyperchloremic acidosis, fluid overload, rhinocerebral mucormycosis, thrombotic events, rhabdomyolysis, and acute respiratory distress syndrome.^{1,6,8,10}

Administration of large doses of insulin for the management of DKA was associated with hypoglycemia, which sometimes was severe. Hypoglycemia is less commonly seen with the use of low-dose insulin regimens and with regular blood glucose monitoring as well as a fluid change to glucose 5% solution when blood glucose falls below 250 mg/dl (13.9 mmol/L).⁸

Hypokalemia can be prevented with appropriate potassium replacement and frequent monitoring. As mentioned above, insulin infusion should be discontinued when serum potassium falls to levels lower than 3.3 mEq/L at any stage of treatment and immediate potassium administration should begin.^{8,10}

Cerebral edema is a very rare complication in adults. It has been described in young adults presenting with DKA and is seen in 1–2% of children presenting with DKA. However, subclinical cerebral edema, demonstrable by computed tomography (CT) scanning or raised cerebrovascular fluid pressure, probably occurs in most cases during or even before treatment.^{10,29} It is manifested by headache,

decline in consciousness level often progressing rapidly to coma, pupillary changes, vomiting, elevated diastolic blood pressure, decorticate or decerebrate posturing, cranial nerve palsies, Cheyne–Stokes respiration, and seizures. Typically it occurs within 8–24 hours after initiation of treatment and many patients deteriorate without warning. The mortality rate is high (70–90%) and may be partially related to delayed diagnosis and treatment. Mechanisms underlying this condition include rapid decline in plasma osmolality (greater than 3% per hour), high intravascular fluid replacement rate, use of hypotonic fluids, and high rate of decrease in blood glucose.^{8,10} The diagnosis can be confirmed by CT or magnetic resonance scanning, which shows swelling of the brain with loss of structural details and squashing of the ventricular system. Treatment of cerebral edema includes administration of mannitol (0.3 g/kg given over 30 minutes and repeated hourly if there is no improvement to single doses of 1 g/kg). Dexamethasone is often given in high doses (4 mg every 6 hours intravenously) but its benefit remains unproven. Mechanical ventilation to remove carbon dioxide and improve acidosis has also been advocated.¹⁰

Non-anion gap hyperchloremic acidosis may occur because chloride is preferentially reabsorbed in the proximal renal tubules and chloride losses are less than sodium losses in DKA. Because replacement solutions have equal amounts of sodium and chloride, relative hyperchloremia may occur with treatment. The development of acidosis should not affect the treatment course and usually resolves.¹⁰

Fluid overload may be seen in patients with severe cardiac or renal impairment. In addition, acute respiratory distress syndrome has been reported in patients less than 50 years of age who are free of cardiac or renal disease. Manifestations include dyspnea, tachypnea, and central cyanosis. Arterial hypoxia is characteristic and chest radiograph reveals bilateral pulmonary infiltrates. The development of new pulmonary rales and an increased alveolar–arterial oxygen gradient are clues to diagnosis. Patients with this syndrome need mechanical support of ventilation and avoidance of fluid overload.^{6,8}

Rhinocerebral mucormycosis may develop in patients who develop recurrent episodes of DKA or another metabolic acidosis. This is caused by an opportunistic fungal infection starting in the paranasal sinuses and rapidly invading adjacent tissues (nose, sinuses, orbit, and brain). Treatment comprises of correction of acidosis, surgical excision of the affected tissues, and intravenous administration of antifungal agents.¹⁰

Diabetes is characterized by a propensity to thrombosis. Marked hyperglycemia is associated with decreased blood flow, increased blood viscosity, and increased coagulability. The role of prophylactic anticoagulation has not been clearly established. Because many patients present with some degree of renal failure, unfractionated heparin use is preferred for prevention of thromboembolism.¹⁰

Rhabdomyolysis is another possible complication of DKA. Hyperosmolality and hypoperfusion contribute to skeletal muscle damage. Recent data suggest that DKA is more common among users of cocaine, a common cause of rhabdomyolysis. Creatinine phosphokinase levels can be initially assessed in patients with DKA if clinically indicated.¹⁰

Summary box

- The most common but preventable complications of DKA are hypoglycemia and hypokalemia
- Rare complications are cerebral edema, non-anion gap hyperchloremic acidosis, fluid overload, rhinocerebral mucormycosis, thrombotic events, rhabdomyolysis, and acute respiratory distress syndrome

Prevention

Many cases of DKA can be prevented by better access to medical care, proper education and effective communication with a health-care provider during an intercurrent illness. Sick-day rules should be reviewed periodically with all patients (see Chapter 8). The patients and/or their family members must be able to determine blood glucose and β -OHB or urine ketones when blood glucose levels are above 300 mg/dl (16.7 mmol/L). Many hospitalizations can be avoided by devoting adequate resources to apply the measures described above.⁸

Summary box

- The majority of DKA cases can be prevented by better access to medical care and proper education
- Sick-day rules must be reviewed periodically with all patients
- All patients with diabetes should be educated to monitor blood or urine for ketones when blood glucose levels are higher than 300 mg/dl (16.7 mmol/L)

Case studies

Case study 1.1

A 32-year-old male with Type 1 diabetes since the age of 14 years was taken to the emergency room because of drowsiness, fever, cough, diffuse abdominal pain, and vomiting. Fever and cough started 2 days ago and the patient could not eat or drink water. He has been treated with an intensive insulin regimen (insulin glargine 24IU at bedtime and a rapid-acting insulin analog before each meal). On examination he was tachypneic, his temperature was 39°C (102.2°F), pulse rate 104 beats per minute, respiratory rate 24 breaths per minute, supine blood pressure 100/70 mmHg; he also had dry mucous membranes, poor skin turgor, and rales in the right lower chest. He was slightly confused. Rapid hematology and biochemical tests showed hematocrit 48%, hemoglobin 14.3 g/dl (143 g/L), white blood cell count 18,000/μl, glucose 450 mg/dl (25.0 mmol/L), urea 60 mg/dl (10.2 mmol/L), creatinine 1.4 mg/dl (123.7 μmol/L), Na^+ 152 mEq/L, K^+ 5.3 mEq/L, PO_4^{3-} 2.3 mEq/L (0.74 mmol/L), and Cl^- 110 mmol/L. Arterial pH was 6.9, PO_2 95 mmHg, PCO_2 28 mmHg, HCO_3^- 9 mEq/L, and O_2sat 98%. The result of the strip for ketone bodies in urine was strongly positive and the concentration of β -OHB in serum was 3.5 mmol/L. Urinalysis showed glucose 800 mg/dl and specific gravity 1030.

What is your diagnosis?

The patient has hyperglycemia, ketosis, and metabolic acidosis. Therefore, he has DKA. In addition, because of the pre-existing fever, cough, localized rales on auscultation and high white blood cell count, a respiratory tract infection should be considered. The patient is also dehydrated and has impaired renal function.

Do you need more tests to confirm the diagnosis?

Determination of the effective serum osmolality and anion gap should be performed in all patients presenting with potential DKA. Serum osmolality can be measured directly in the laboratory or be calculated. Calculated effective serum osmolality in this case was 329 mOsm/kg and the anion gap is 33 mEq/L. Typically DKA is a high anion gap metabolic acidosis while serum osmolality may vary from normal to high. In addition a chest X-ray should be performed and blood cultures be obtained to check for lower respiratory tract infection and isolate the pathogenic bacteria.

How will you manage this patient?

Immediate infusion of normal saline and intravenous insulin should be initiated as described in the text. Because his serum potassium level is in the normal range, 10mEq of potassium should be added to each liter of normal saline infused. Serum potassium levels should be checked at 2, 6, 10, and 24 hours and appropriate adjustment to the dose must be made. In addition, 100ml of bicarbonate plus 10mEq of potassium in 200 ml of water can be administered in 1 hour because pH is 6.9 and plasma bicarbonate levels are low. Arterial pH and bicarbonate should be re-checked in 30 minutes and, if uncorrected, infusion of a similar or lower amount of bicarbonate should be repeated as discussed in the text. If infection is confirmed, intravenous administration of antibiotics should begin while waiting for the results of blood cultures.

The patient was treated with fluids and electrolyte replacement and intravenous insulin for 48 hours. Afterwards, his blood glucose was 150mg/dl (8.3mmol/L), fever, nausea, vomiting and abdominal pain resolved, and he was able to eat and to drink water.

What is your next step?

The patient can start to eat and drink water. Intravenous insulin can safely be discontinued and subcutaneous insulin begun. A bolus of rapid-acting insulin should be administered subcutaneously based on the results of the fingerstick test 1–2 hours before discontinuation of intravenous insulin, and 24IU of basal insulin should be started.

A careful history should be obtained to determine the cause of DKA and to avoid recurrence. This patient was not aware of the sick-day rules and had never been instructed to check often or how to correct high blood glucose values. Because he was not able to eat and drink water he reduced both the basal and the preprandial insulin to avoid hypoglycemia. The patient was educated about sick-day rules and to check urine and blood for ketones if blood glucose is above 300mg/dl (16.7mmol/L).

Case study 1.2

An 18-year-old female was taken to the emergency room in coma. Her parents noticed that she had polydipsia, polyuria, and rapid weight loss which started approximately 1 month ago and had worsened in the last week. She had not been taking any

medications and the clinical history was otherwise unremarkable. On examination, breathing was deep and rapid (Kussmaul respiration), pulse rate was 100 beats per minute, and blood pressure 110/70 mmHg; she also had signs of dehydration. She was drowsy and confused. Rapid hematology and biochemical tests showed hematocrit 44%, hemoglobin 13 g/dl (140 g/L), white blood cell count 12,000/ μ l, glucose 520 mg/dl (28.9 mmol/L), urea 50 mg/dl (8.5 mmol/L), creatinine 0.8 mg/dl (70.7 μ mol/L), Na^+ 148 mEq/L, K^+ 4.6 mEq/L, PO_4^{3-} 2.0 mEq/L (0.64 mmol/L), and Cl^- 112 mmol/L. Arterial pH was 7.0, PO_2 98 mmHg, PCO_2 25 mmHg, HCO_3^- 12 mEq/L, and O_2sat 98%.

What is your diagnosis?

The patient has marked hyperglycemia and metabolic acidosis. The diagnosis of newly diagnosed Type 1 diabetes presenting with DKA should be considered.

Which additional biochemical tests are required to confirm the diagnosis?

Determination of ketone bodies in blood or urine is necessary to confirm ketosis. In this case the strip for ketones in the urine was strongly positive and determination of β -OHB in serum was 4.0 mmol/L. Thus, the patient has the triad of hyperglycemia, ketosis, and acidosis and the diagnosis of DKA is confirmed.

How will you manage the patient?

Urgent administration of intravenous fluid and insulin should begin together with careful monitoring, replacement of electrolytes, and correction of acidosis. After resolution of DKA and as long as the patient is conscious, feeding can start. Transition from intravenous to subcutaneous insulin administration should begin. A bolus of rapid-acting insulin should be administered subcutaneously based on the results of the fingerstick test 1–2 hours before discontinuation of intravenous insulin. A total daily dose of insulin of 0.5–0.8 IU/kg is required, divided as 30–50% basal insulin and the remainder as rapid-acting insulin before each meal.

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CHAPTER 2

Diabetic ketoacidosis in childhood and adolescence

Christina Kanaka-Gantenbein

Definition of emergency

Diabetic ketoacidosis (DKA) is the leading cause of morbidity and mortality in children with Type 1 diabetes mellitus (T1D). Mortality is mainly related to the occurrence of cerebral edema, while only a minority of deaths are attributed to other causes.^{1,2}

Diabetic ketoacidosis is attributed to the combination of absolute or relative insulin deficiency with excess of counter-regulatory hormones, including glucagon, growth hormone, catecholamines, and cortisol.^{1–3} It is well known that insulin is the only glucose-lowering hormone of the body, permitting the influx of glucose into the cells for energy production and facilitating lipid formation, while all other hormones, the so-called “counter-regulatory hormones”—growth hormone, glucagon, catecholamines, and cortisol—exert an opposing action, facilitating glucose formation through gluconeogenesis and glycogenolysis. The combination of low serum insulin with increased counter-regulatory hormones thus results in a catabolic state with increased glucose production and diminished peripheral glucose utilization, causing hyperglycemia and hyperosmolality and enhanced lipid oxidation, resulting in increased lipolysis and ketogenesis and ultimately leading to ketonemia and metabolic acidosis.^{3,4} The pathophysiology of diabetic ketoacidosis is illustrated in Figure 1.1. The combination of hyperglycemia, which drives water transport from the intracellular compartment

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to the intravascular one and finally through enhanced urinary perfusion leads to enhanced osmotic diuresis causing hyperosmotic dehydration, with metabolic acidosis, may be life-threatening if left undiagnosed and not adequately managed. The ketoacidosis may even be aggravated by supervening lactic acidosis, because of poor tissue perfusion, while the osmotic diuresis results in electrolyte losses that may cause further life-threatening disturbances such as cardiac arrhythmias.¹⁻⁴

At presentation, the magnitude of specific deficits in the individual patient varies, depending on the duration and severity of symptoms and dehydration, until the individual patient comes to medical attention and receives adequate treatment.

The epidemiology, potential causes, and clinical manifestations as well as management of DKA presented in this chapter are based on the recent international consensus statements of the most appropriate scientific societies in this field such as the European Society for Pediatric Endocrinology (ESPE), the Lawson Wilkins Society for Pediatric Endocrinology (LWSPE), the American Diabetes Association (ADA), and the International Society for Pediatric and Adolescent Diabetes (ISPAD). The recommendations for the management of DKA were first published in both *Pediatrics* and *Archives of Disease in Childhood* in 2004,^{1,2} then as a consensus statement of the American Diabetes Association in 2006,³ and more recently in the Compendium of the ISPAD Clinical Practice Consensus Guidelines 2009 in *Pediatric Diabetes* in 2009.⁴

The consensus statements with their worldwide evidence- and expert-based recommendations on diabetic ketoacidosis in children and adolescents¹⁻⁴ are greatly respected and are presented in detail here. Their management recommendations are summarized in Figure 2.1. It has to be noted, however, that although guidelines are considered to be useful for the majority of cases, individualization in decision making and treatment modalities may also be necessary.

Potential causes

DKA is usually the first manifestation in an undiagnosed case of Type 1 diabetes mellitus (T1D), especially in toddlers, while it may also occur in a poorly controlled Type 1 diabetic patient, either due to concurrent disease or insulin omission.^{3,4} Diabetic children and adolescents treated by continuous subcutaneous insulin infusion (insulin pump) are more prone to develop DKA if a technical

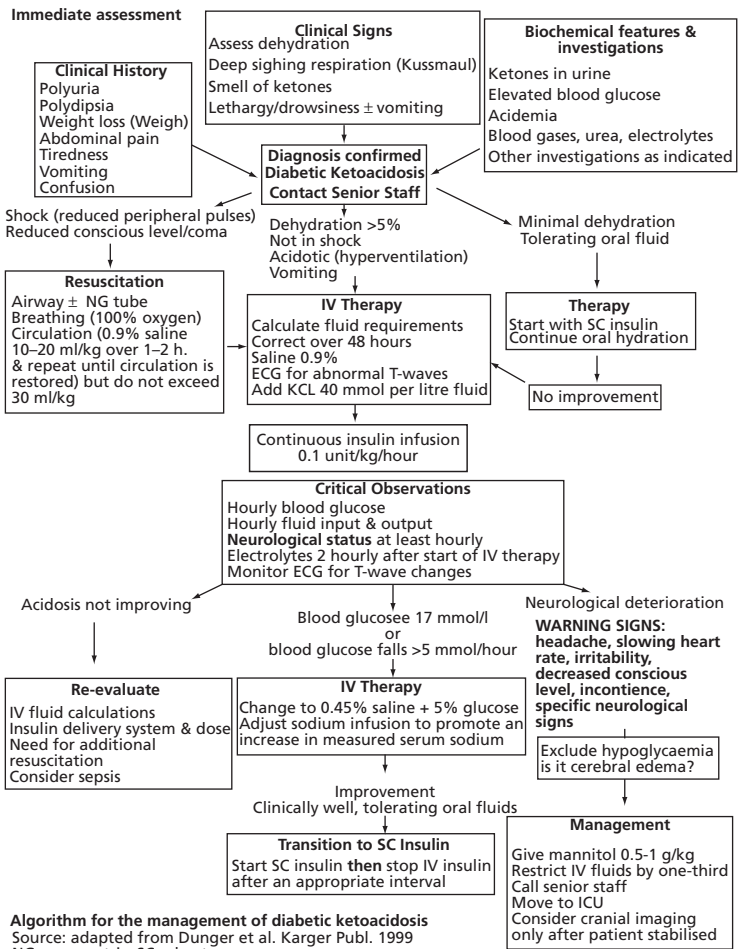


Figure 2.1 Algorithm for the monitoring and management of diabetic ketoacidosis. From Wolfsdorf J et al. Pediatric Diabetes 2009; 10 (suppl. 12):128 [4], with permission.

problem in the pump supervenes, since there is no circulating long-acting insulin in the body and insulin deficiency leads quickly to metabolic decompensation.^{3–5}

Most cases of DKA are therefore observed in T1D patients.^{4,6,7} However, the significant increase in childhood and adolescent obesity worldwide has led to an increase in Type 2 diabetes (T2D)

incidence, especially during adolescence and more frequently in some ethnic groups such as African-Americans and less frequently in Hispanics, while it is still rare among Caucasian whites. In the ethnic minorities that present a high incidence of T2D, DKA may be the first manifestation of Type 2 diabetes in up to 25% of cases. Overall, however, only about 5% of T2D cases are first manifested by DKA.^{4,8,9}

Epidemiology

There is a wide geographic variation in the frequency of DKA at diabetes onset, ranging from 10 to 70% of cases in Europe and North America. Rates of DKA were suggested to be higher in areas where T1D incidence is lower and therefore suspicion for the occurrence of T1D is weaker. However, recent epidemiological studies have documented a continuing high incidence of DKA among new-onset T1D patients, even in areas where the annual incidence of T1D has significantly increased during the last decades (Figure 2.2).^{4,6,7} Moreover, the frequency of DKA is higher among younger children, reaching an incidence of almost 60% among children younger than 2 years of age, and averaging 25% in those younger

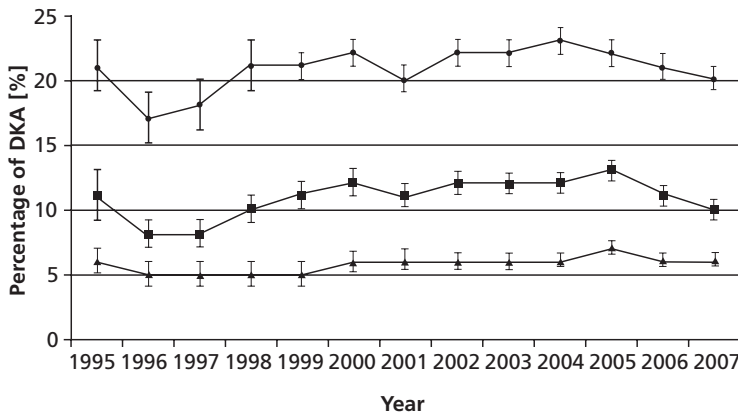


Figure 2.2 Frequency of diabetic ketoacidosis and its severity during a 13-year observation period—a multicenter analysis of 14,664 patients from 106 institutions. Frequency of DKA according to years. ●, pH <7.3; ■, pH <7.2; ▲, pH <7. Copyright 2009 American Diabetes Association. From *Diabetes Care*, Vol. 32, 2009; 1647–1648. Reproduced by permission of The American Diabetes Association.

than 4 years of age worldwide, especially in areas where medical care is less accessible. Therefore, both older retrospective studies and recent prospective studies have revealed a high incidence of DKA among newly diagnosed T1D patients, especially in the very young, even in areas with an increased overall incidence of T1D.^{6,7,10,11}

Diagnosis

The diagnosis is mainly based on biochemical criteria, while clinical presentation may vary depending on the duration until the patient seeks medical assistance.⁴

The biochemical criteria for the diagnosis of diabetic ketoacidosis are:

- Hyperglycemia (blood glucose >200 mg/dl [11 mmol/L])
- Acidosis (venous pH < 7.3 or bicarbonate < 15 mmol/L)
- Ketonemia and ketonuria.

Laboratory investigations may also reveal:

- Leukocytosis with a left shift
- Non-specific serum amylase elevation.

DKA is generally categorized by acidosis, varying from mild to severe:

- Mild: venous pH < 7.3 but still > 7.2 and bicarbonate concentration 10–15 mmol/L
- Moderate: venous pH ranging from 7.1 to 7.2 and bicarbonate concentration 5–9 mmol/L
- Severe: venous pH < 7.1 and bicarbonate concentration < 5 mmol/L.^{1–4}

The clinical manifestations of diabetic ketoacidosis are:

- Dehydration
- Rapid, deep sighing (Kussmaul respiration)
- Nausea, vomiting, and abdominal pain, mimicking an acute abdomen
- Progressive dizziness, lethargy, and loss of consciousness
- Fever, only when infection is present.

Clinical management

Emergency assessment

First of all, the patient should be clinically assessed to define the severity of dehydration, the level of consciousness, the presence of vomiting, etc.⁴

Table 2.1 Glasgow coma scale

Best eye response	Best verbal response	Best verbal response (non-verbal children)	Best motor response
1. No eye opening	1. No verbal response	1. No response	1. No motor response
2. Eyes open to pain	2. No words, only incomprehensible sounds; moaning	2. Inconsolable, irritable, restless, cries	2. Extension to pain (decerebrate posture)
3. Eyes open to verbal command	3. Words, but incoherent*	3. Inconsistently consolable and moans; makes vocal sounds	3. Flexion to pain (decorticate posture)
4. Eyes open spontaneously	4. Confused, disoriented conversation [†]	4. Consolable when crying and interacts inappropriately	4. Withdrawal from pain
	5. Orientated, normal conversation	5. Smiles, oriented to sound, follows objects, and interacts	5. Localizes pain 6. Obeys commands

*Inappropriate words, random or exclamatory articulated speech, but no sustained conversational exchange.

[†]Attention can be held; patient responds to questions coherently, but there is some disorientation and confusion.

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The level of consciousness can be assessed using the Glasgow coma scale (Table 2.1), although clinical common sense is usually adequate.

Clinical assessment of the severity of dehydration may quite often be inaccurate and imprecise.^{4,12,13} The three most useful signs to assess at least 5% dehydration and acidosis in young children are:

- Prolonged capillary refill time (normal capillary refill time is <1.5–2 seconds)
- Abnormal skin turgor
- Hyperpnea.

Further signs of dehydration are:

- Sunken eyes
- Dry mucous membranes

- Absent tears
- Weak pulses
- Cool extremities.

Initial laboratory assessment

Obtain a blood sample for determination of blood glucose, electrolytes (sodium, potassium, chloride) blood urea nitrogen, venous pH, PCO_2 , HCO_2 , anion gap, calcium, phosphorus, magnesium, complete blood count for determination of hemoglobin, hematocrit, leukocytes. It has, however, to be mentioned that phosphorus, calcium, and magnesium levels are less important for treatment.

Obtain a urine sample to check for ketones and to ascertain diuresis.

If clinically indicated, perform ECG monitoring to check for possible abnormalities as a response to electrolyte changes.

If clinical suspicion of an intercurrent infection exists, obtain specific samples for culture, for example blood and urine specimens.

A child with diabetic ketoacidosis should be managed in a unit that has:

- Experienced nursing staff trained in monitoring and management
- Written guidelines for DKA management based on international guidelines
- Access to laboratories for frequent and timely biochemical measurements
- A specialist/consultant pediatrician with training and expertise in managing DKA in children, who should supervise initial inpatient management.

A child with severe DKA or depressed level of consciousness may be managed in a pediatric intensive care unit, if enough expertise is available.

Supportive measures

- Secure the airway, if necessary.
- A peripheral intravenous catheter should be sited for frequent venous sampling and two further intravenous routes should be placed to cover fluid and insulin administration.
- Cardiac monitoring may be necessary to check for changes due to potassium alterations.
- Oxygen administration may be needed.
- Antibiotic administration may be indicated in a febrile patient, after specific body fluid samples for culture have been obtained.

- Bladder catheterization is not usually indicated in a pediatric patient with DKA, but may be necessary when the patient is unconscious or urine output cannot otherwise be monitored.

Monitoring

Successful management of DKA requires meticulous and close monitoring.⁴ Monitoring of the patient should be documented on a flowchart, where clinical assessment and fluid and insulin administration should be registered hourly and laboratory results should be documented when available. Monitoring should include (Figure 2.1):

- Vital signs (pulse rate, blood pressure, respiratory rate): hourly
- Neurological observation for early detection of the occurrence of signs and symptoms of cerebral edema, the most serious complication of DKA (discussed in detail below): hourly
- Amount of insulin administered: hourly
- Accurate fluid input and, if indicated, output: hourly
- Capillary blood glucose measurement, verified by laboratory blood glucose measurement, since capillary readings may be inaccurate in extreme high or low glucose values and because of poor peripheral circulation: hourly
- Biochemical laboratory tests for determination of plasma electrolytes, blood glucose, blood urea nitrogen, calcium, magnesium, and phosphorus, as well as blood gases and hematocrit: every 2 hours at the beginning, or more frequently in severe cases, and gradually monitored less frequently upon stabilization of the patient
- Urine ketones: until cleared.

First-line management

The goals of first-line management of DKA are outlined in Box 2.1:⁴

Box 2.1 Goals of treatment

- Correct dehydration
- Correct acidosis and reverse ketosis
- Restore blood glucose to near normal values
- Avoid complications, such as cerebral edema
- Identify and treat any precipitating event

Correction of dehydration

Pediatric patients with DKA have a deficit of extracellular fluid volume of around 5–10%. Since clinical assessment of the volume deficit is inaccurate and subjective, it is usual to calculate 5–7% deficit in moderate DKA and about 7–10% fluid deficit in severe DKA.^{12,13}

Increased serum urea nitrogen and hematocrit can be useful markers of the severity of extracellular fluid contraction. On the other hand, serum sodium levels are factitious, mainly because of a water shift from the intracellular compartment to the intravascular one due to the osmotic action of high glucose concentrations.^{14,15} Therefore, one has to calculate the corrected sodium concentration using the following formula⁴:

Corrected sodium concentration

$$= \text{measured Na} + 2([\text{plasma glucose in mmol/L} - 5.6]/5.6).$$

where 1 mmol/L of glucose corresponds to 18 mg/dl.

Upon fluid and insulin administration, plasma glucose levels will decrease and the measured sodium concentration is expected to increase. A failure of serum sodium levels to increase or a further decline in levels is a potentially ominous sign of impending cerebral edema.^{4,16,17}

The principles of fluid administration are as follows:

- Water and salt deficits must be replaced, but it is important to replace fluid deficits slowly over 48 hours.
- Intravenous or oral fluids that may have been given in another facility before assessment should be factored into calculations of deficit and repair.
- For patients who are not severely dehydrated, volume expansion should start with 0.9% saline.
- For patients who are severely volume depleted, but not in shock, volume expansion should begin immediately with 0.9% saline to restore the peripheral circulation.
- In the rare patient with DKA who presents in shock, rapidly restore circulatory volume with isotonic saline in 20 ml/kg boluses infused as quickly as possible with reassessment after each bolus.
- The volume and rate of administration depends on circulatory status and, where it is clinically indicated, the volume administered is 10 ml/kg per hour, repeated if necessary.

- *Use crystalloid, not colloid!* There are no data to support the use of colloid in preference to crystalloid in the treatment of DKA.
- Subsequent fluid management should be with 0.9% saline (or Ringer's) for at least 4–6 hours.
- Thereafter, deficit replacement should be with a solution that has a tonicity equal to or greater than 0.45% saline with added potassium chloride, potassium phosphate, or potassium acetate.
- The rate of fluid (IV and oral) should be calculated to rehydrate evenly over 48 hours. It might be dangerous to cover the fluid deficit in a few hours.
- Remember to provide potassium in the fluids administered as soon as urine output has been documented or even earlier in the hypokalemic patient, as is discussed in detail below.
- In addition to clinical assessment of dehydration, calculation of effective osmolality may be valuable to guide fluid and electrolyte therapy, according to the following formula:⁴

$$\text{Effective osmolality (in mOsm/kg)} = 2 \times (\text{Na} + \text{K}) + \text{glucose (in mmol/L)}$$

- Urinary losses should not routinely be added to the replacement fluid calculation, but this may be necessary in rare circumstances.
- The sodium content of the fluids may rarely need to be increased if measured serum sodium is low and does not rise appropriately as the plasma concentration falls. However, the use of large amounts of 0.9% saline has been associated with the development of hyperchloremic metabolic acidosis.¹⁸
- In practice, the fluids administered are calculated as the sum of fluid losses (usually a fluid deficit of 5–10% exists) plus the maintenance fluid requirement for 48 hours, evenly distributed over 48 hours, as illustrated in Tables 2.2a and b.

Insulin administration (Box 2.2)

“Low dose” IV insulin infusion should be the standard care in treating DKA. Most protocols, including the consensus guidelines, support the IV administration of 0.1 IU/kg per hour of regular insulin, although very recent studies comparing an initial dose of 0.1 versus 0.05 IU/kg per hour have demonstrated similar rates of improvement of DKA patients.^{4,19,20} In clinical practice, it is adequate to start with an insulin dose of 0.08 IU/kg per hour and diminish accordingly as the acidosis subsides. In very young patients,

Table 2.2a Calculation of fluids and electrolytes to be administered during the management of DKA. The total amount of losses in addition with the 2-days' 24-hour maintenance requirements should be evenly given over 48 hours

	Average (range) losses per kg	24-hour maintenance requirements	
Water	70 ml (30–100)	* ≤ 10 kg	100 mL/kg/24 h
		11–20 kg	1000 mL + 50 mL/kg/24 hr for each kg from 11–20
		>20 kg	1500 mL + 20 mL/kg/24 hr for each kg >20
Sodium	6 mmol (5–13)		2–4 mmol [†]
Potassium	5 mmol (3–6)		2–3 mmol
Chloride	4 mmol (3–9)		2–3 mmol
Phosphate	(0.5–2.5) mmol		1–2 mmol

Data are from measurements in only a few children and adolescents. In any individual patient, actual losses may be less or greater than the ranges shown.

[†]Maintenance electrolyte requirements in children are per 100 ml of maintenance IV fluid following the Holliday-Segar formula of fluid requirements calculation according to body weight.

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Table 2.2b Calculation of fluids to be administered during the management of DKA

Body weight kg	Maintenance ml/24 h	DKA: Give maintenance + 5% of body weight/24-h	
		ml/24 h	ml/h
4	325	530	22
5	405	650	27
6	485	790	33
7	570	920	38
8	640	1040	43
9	710	1160	48
10	780	1280	53
11	840	1390	58
12	890	1490	62

Continued

Table 2.2b (*Continued*)

Body weight kg	Maintenance ml/24 h	DKA: Give maintenance + 5% of body weight/24-h	
		ml/24 h	ml/h
13	940	1590	66
14	990	1690	70
15	1030	1780	74
16	1070	1870	78
17	1120	1970	82
18	1150	2050	85
19	1190	2140	89
20	1230	2230	93
22	1300	2400	100
24	1360	2560	107
26	1430	2730	114
28	1490	2890	120
30	1560	3060	128
32	1620	3220	134
34	1680	3360	140
36	1730	3460	144
38	1790	3580	149
40	1850	3700	154
45	1980	3960	165
50	2100	4200	175
55	2210	4420	184
60	2320	4640	193
65	2410	4820	201
70	2500	5000	208
75	2590	5180	216
80	2690	5380	224

After initial resuscitation, and assuming 10% dehydration, the total amount of fluid should be given over 48 hours. The table gives volumes for maintenance and rehydration per 24 hours and per hour. If fluid has been given for resuscitation, the volume should **not** be subtracted from the amount shown in the table. Fluids given orally (when patient has improved) **should** be subtracted from the amount in the table. For body weights >32kg, the volumes have been adjusted so as not to exceed twice the maintenance rate of fluid administration.

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Box 2.2 Main principles of insulin administration

- Start insulin infusion 1–2 hours *after* starting fluid replacement therapy
- Insulin therapy is necessary not only to lower blood glucose levels but more importantly to suppress lipolysis and ketogenesis and therefore to eliminate metabolic acidosis
- *An IV insulin bolus administration in children is unnecessary, since it may increase the risk of cerebral edema, and should not be used at the initiation of treatment*

it is more prudent to start with 0.05 IU/kg per hour IV insulin administration.

- *An IV insulin bolus administration should be avoided.*^{4,21,22}
- The dose of insulin should invariably remain at the initial rate at least until resolution of DKA (pH > 7.30, bicarbonate >15 mmol/L and/or normalization of the anion gap), which invariably takes longer than normalization of the blood glucose concentrations.
- If the patient demonstrates marked sensitivity to insulin (for example very young patients, as reported above) the dose may be decreased to 0.05 IU/kg per hour, or less, provided that metabolic acidosis continues to resolve.

Modification of insulin/fluid administration in specific cases

- During initial volume expansion the plasma glucose concentration falls steeply. Thereafter, and after initiation of insulin administration, the plasma glucose concentration typically decreases at a rate of 36–90 mg/dl (2–5 mmol/L), depending on the timing and amount of glucose administration. To prevent an unduly rapid decrease of plasma glucose concentration and the risk of hypoglycemia, 5% glucose should be added to the IV fluid (e.g., 5% glucose in 0.45% saline) when the plasma glucose falls to approximately 250–300 mg/dl (14–17 mmol/L), or sooner if the rate of blood glucose fall is steeper. It may even rarely be necessary to infuse 10–12.5% dextrose in order to prevent hypoglycemia while continuing to infuse insulin to correct the metabolic acidosis.⁴
- If blood glucose falls very rapidly (>5 mmol/L) after initial fluid expansion, consider adding glucose even before plasma glucose has decreased to 300 mg/dl (17 mmol/L).

- If biochemical parameters of DKA (pH, anion gap) do not improve, reassess the patient, review insulin therapy, and consider other possible causes for poor response such as inadequate fluid or insulin infusion at the infusion site, etc.
- If IV insulin administration is not possible, consider subcutaneous (or even IM) administration of rapid-acting analogs, such as lispro or aspart at 1- to 2-hour intervals. The insulin dose should be initially 0.3 IU/kg, followed 1 hour later by 0.1 IU/kg of insulin lispro or aspart SC hourly or at a dose of 0.15–0.2 IU/kg every 2 hours.
- If blood glucose falls to <250 mg/dl (14 mmol/L) before DKA has resolved (pH still <7.30), add 5% glucose solution IV and continue insulin as above.
- It is prudent to keep blood glucose at a level of about 200 mg/dl (11 mmol/L) until resolution of DKA.

Potassium replacement

Children with DKA suffer total body potassium deficits in the range of 3–6 mmol/L, mainly due to intracellular compartment depletion.⁴ However, at initial presentation serum potassium levels may be normal, decreased, or even elevated.²³ Administration of insulin and correction of acidosis will drive potassium back into the cells, decreasing serum levels.⁴ Therefore:

- *Potassium replacement therapy is necessary regardless of the initial serum potassium concentration.*
- If the patient is already hypokalemic at presentation, potassium administration should be initiated immediately at the time of initial volume expansion before starting insulin administration.
- If the patient is hyperkalemic, defer potassium replacement therapy until urine output has been documented.
- The starting potassium concentration in the infusate should be 40 mmol/L and subsequently adjusted according to biochemical serum potassium measurements. Potassium phosphate may be used together with potassium chloride or potassium acetate, especially when critically low serum phosphate levels have been documented. However, in clinical practice, phosphate supplementation is rarely needed and serum phosphate levels return to normal upon resolution of acidosis.^{24–27}
- Potassium replacement should be continued throughout IV fluid therapy.

- If hypokalemia persists despite maximum rate of potassium replacement, then a reduction in insulin infusion rate should be considered and eventually extra potassium administration should be initiated.

ECG findings in potassium disorders are as follows.

- ECG findings in hypokalemia:
 - Flattening of the T wave
 - Widening of the QT interval
 - Appearance of U waves
- ECG findings in hyperkalemia:
 - Tall, peaked, symmetrical T waves
 - Shortening of the QT interval.

Acidosis management

Severe acidosis is reversible by fluid and insulin replacement. Insulin stops lipolysis and further ketone production and allows ketoacids to be metabolized, generating bicarbonate.⁴ Moreover, treatment of hypovolemia improves tissue perfusion and renal function, thereby increasing the excretion of organic acids.

Controlled trials have shown no clinical benefit from bicarbonate administration^{3,4} and there are well-recognized serious adverse effects, including paradoxical CNS acidosis^{28,29} and hypokalemia from rapid acidosis correction.^{30,31} Nevertheless, there may be selected patients who may profit from cautious alkali administration, such as patients with severe acidemia (arterial pH <6.9) in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion, and patients with life-threatening hyperkalemia.^{4,32}

If bicarbonate is considered necessary, cautiously give 1–2 mmol/kg over 60 minutes.^{3,4}

Follow-up management-transition to per os fluid intake and SC insulin injections

- Oral fluids should be introduced only when substantial clinical improvement has occurred and when oral fluids are well tolerated; IV fluid administration should then be reduced.
- The most convenient time to change to SC insulin is just before a mealtime, provided that ketoacidosis has resolved (venous pH > 7.3 and serum bicarbonate >18 mmol/L), plasma glucose is <200 mg/dl (11.1 mmol/L), and oral fluid intake is well tolerated.

- To prevent rebound hyperglycemia, the first SC insulin injection should be given 15–30 minutes (with rapid-acting insulin analog) or 1–2 hours (with regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed. With intermediate or long-acting insulin the overlap should be longer and the IV insulin gradually lowered. For example, for patients on a basal-bolus insulin regimen, the first dose of basal insulin should be administered in the evening and the insulin infusion should be stopped the next morning.
- There is no clear advantage of one SC insulin regimen over the other when changing from IV to SC insulin, and the dose and type of insulin should be according to local preferences and circumstances.^{3,4} One possible insulin regimen for newly diagnosed diabetes after resolution of DKA is to provide two thirds of the total daily insulin requirement in the morning 30 minutes before breakfast, divided as two thirds intermediate-acting insulin and one third rapid-acting insulin, and the remaining one third of the daily requirement in the evening 30 minutes before dinner, again dividing the dose as two-thirds intermediate-acting insulin and one third rapid-acting. When the decision has been made to start an insulin analog regimen, 40–50% of daily insulin requirement is provided before going to bed as a long-acting analog (glargine or detemir), while the remaining insulin requirement is divided into doses of a rapid-acting analog 10–15 minutes before meals. Type 1 diabetic patients who were already on an insulin regimen (for example insulin pump or basal-bolus principle) before the occurrence of DKA can go back on their usual regimen.
- After transition to SC insulin, frequent blood glucose monitoring is required to avoid marked hyper- or hypoglycemia.

Potential complications—morbidity and mortality

The overall mortality rate from DKA in children is 0.15–0.30%.^{3,4,22}

Cerebral edema

The most severe potential complication of DKA management is cerebral edema. It accounts for 60–90% of all DKA deaths.^{3,4,16,22} Although rare, when it supervenes it is accompanied by a mortality rate of 21–24%. Moreover, 10–25% of survivors of cerebral edema have significant residual morbidity. Despite considerable efforts to

identify the potential cause of cerebral edema, its pathogenesis is incompletely understood and there is evidence that some cerebral edema cases supervene even before the initiation of DKA treatment.¹⁶ There is no convincing evidence of an association between the rate of fluid or sodium administration used in the treatment of DKA and the development of cerebral edema.^{4,33} Patients more likely to develop cerebral edema are:

- The young
- Those with new-onset diabetes
- Those with a longer duration of symptoms.

The signs and symptoms of cerebral edema are:

- Headache and slowing of heart rate
- Change in neurological status (restlessness, irritability, increased drowsiness, incontinence)
- Specific neurological signs (e.g., cranial nerve palsies)
- Rising blood pressure
- Decreased O₂ saturation.

Risk factors for the development of cerebral edema at diagnosis or during treatment of DKA have been reported to be:^{4,16}

- Greater hypocapnea at presentation after adjusting for the degree of acidosis^{16,34}
- Increased serum urea nitrogen at presentation^{16,34}
- More severe acidosis at presentation^{22,35}
- Bicarbonate treatment for correction of acidosis¹⁶
- An attenuated rise in measured serum sodium concentration during therapy³⁶
- Greater volumes of fluid given in the first 4 hours^{4,22}
- Administration of insulin during the first hour of fluid treatment.²²

In recent studies, the degree of edema formation during DKA in children correlated with the degree of dehydration and hyperventilation at presentation, but not with factors related to initial osmolality or osmotic changes during treatment.⁴ These data have been interpreted as supporting the hypothesis that cerebral edema is related to cerebral hypoperfusion during DKA and that osmotic fluctuations during DKA treatment do not play a primary causal role.^{4,34}

Clinically significant cerebral edema usually occurs 4–12 hours after treatment has started, but can even occur before treatment initiation,^{4,16} or, rarely, may develop as late as 24–48 hours after initiation of treatment.

Box 2.3 Criteria used for the diagnosis of cerebral edema**Diagnostic criteria**

- Abnormal motor or verbal response to pain
- Decorticate or decerebrate posture
- Cranial nerve palsy (especially III, IV, and VI)
- Abnormal neurogenic respiratory pattern (e.g. grunting, tachypnea, Cheyne–Stokes respiration, apneusis)

Major criteria

- Altered mentation/fluctuating level of consciousness
- Sustained heart rate deceleration (decrease more than 20 beats per minute) not attributable to improved intravascular volume or sleep state
- Age-inappropriate incontinence

Minor criteria

- Vomiting
- Headache
- Lethargic or not easily arousable
- Diastolic blood pressure >90 mmHg
- Age <5 years

The criteria used for the diagnosis of cerebral edema are categorized as major or minor (Box 2.3).^{4,37} Thus, one diagnostic criterion, two major criteria, or one major and two minor criteria have a sensitivity of 92% to diagnose cerebral edema and a false positive rate of only 4%.

Treatment of cerebral edema

- Initiate treatment as soon as the condition is suspected.
- Mannitol or hypertonic saline should be available at the bedside.
- Reduce the rate of fluid administration by one third.
- Give mannitol 0.5–1 g/kg IV over 20 minutes and repeat if there is no initial response in 30 minutes to 2 hours.^{4,38} *Note, however, that mannitol may result in rebound cerebral edema!*
- Hypertonic saline (3%) 5–10 ml/kg over 30 minutes may be an alternative to mannitol or a second-line therapy if there is no initial response to mannitol.^{4,39}

Box 2.4 Potential complications—causes of important morbidity and mortality in DKA

- Cerebral edema
- Hypokalemia
- Hyperkalemia
- Severe hypophosphatemia
- Severe hypoglycemia
- Other CNS complications (disseminated intravascular coagulation, dural sinus thrombosis, basilar artery thrombosis)
- Peripheral venous thrombosis
- Sepsis
- Rhinocerebral or pulmonary mucormycosis
- Aspiration pneumonia
- Pulmonary edema
- Acute respiratory distress syndrome (ARDS)
- Pneumothorax, pneumomediastinum, subcutaneous emphysema
- Rhabdomyolysis
- Acute renal failure
- Acute pancreatitis

- Elevate the head of the bed.
- Intubation may be necessary for the patient with impending respiratory failure, but aggressive hyperventilation (to a $\text{PCO}_2 < 2.9 \text{ kPa}$ [22 mmHg]) has been associated with poor outcome and is not recommended.
- After treatment for cerebral edema has been started, a cranial CT scan should be obtained to rule out other possible intracerebral causes of neurological deterioration (about 10% of cases), especially thrombosis or hemorrhage, which may benefit from specific therapy.^{40,41}

Box 2.4 summarizes all possible complications and causes of morbidity and mortality after DKA in children.

Prevention of recurrent DKA

It is important to clarify the causes of an episode of DKA, especially in patients known to have diabetes, in order to avoid a subsequent episode.

- In most cases, insulin omission, either inadvertent or deliberate, is the cause of DKA.
- There is usually an important psychosocial reason for insulin omission
 - in an adolescent girl an attempt to lose weight
 - a means of escaping an intolerable home situation
 - the result of clinical depression

and trial of a multisystematic psychotherapeutic approach may lead to reduction of new episodes of DKA in poorly controlled type 1 diabetic adolescents (Figure 2.3).⁴²

- Specifically in insulin pump users, the most common cause of DKA is the failure to take extra insulin using a pen or a syringe when hyperglycemia and hyperketonemia or ketonuria occur due to technical problems with the pump such as catheter occlusion, etc.
- An infection that is not associated with vomiting or diarrhea is seldom the cause of DKA when the patient and the whole family

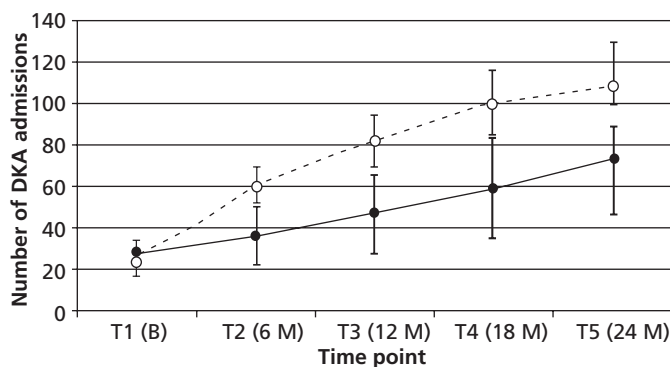


Figure 2.3 The impact of a multisystematic approach in diminishing the incidence of episodes of diabetic ketoacidosis in adolescents with poorly controlled Type 1 diabetes mellitus. Cumulative number of DKA admissions during five 6-month intervals for MST (●) and control (○) participants. The baseline interval (T1) started 6 months before trial entry; the subsequent intervals were from T1 to treatment termination (T2), from treatment termination to 12-month follow-up (T3), from 12-month to 18-month follow-up (T4), and from 18-month to 24-month follow-up (T5). Error bars are ± 1 SE. Copyright 2008 American Diabetes Association. From *Diabetes Care*, Vol. 31, 2008; 1746–1747. Reproduced by permission of The American Diabetes Association.

are well educated in diabetes management and there is a 24-hour telephone helpline available.⁴³

Summary box

- It is important that children and adolescents with DKA should be managed in centers experienced in treating DKA
- It is important that general practitioners and all health professionals have a high level of suspicion to recognize and diagnose a case of DKA early in order to prevent severe metabolic deterioration and loss of consciousness
- It is important to begin fluid replacement therapy 1–2 hours *before starting* insulin therapy
- Volume expansion is required only if needed to restore peripheral circulation, and subsequent fluid administration (including oral fluids) should *rehydrate evenly over 48 hours* at a rate rarely in excess of 1.5–2 times the usual daily maintenance requirement
- If the blood glucose concentration decreases too quickly or becomes too low before DKA has resolved, increase the amount of glucose administered. *Do not decrease the insulin infusion*
- *Even with normal or high levels of serum potassium at presentation, there is always a total body deficit of potassium*
- *There is no evidence that bicarbonate is either necessary or safe in DKA*
- *All cases of recurrent DKA are preventable*
- Abdominal pain mimicking acute abdomen in childhood may be a symptom of DKA and not necessarily of appendicitis

Patient advice

- Always check your blood glucose levels, especially when you are ill.
- Besides blood glucose measurements, check for the presence of ketones in urine, or even better in plasma, when you are sick and have high blood glucose readings. The presence of ketones in combination with high blood glucose readings suggests that you are at risk for decompensation, i.e. for diabetic ketoacidosis.
- Always have a pen of rapid-acting and long-acting insulin analog available, even if you wear an insulin pump, since technical problems with the insulin pump or the catheter may lead to diabetic ketoacidosis if they are not quickly reversed and treated.

- *Remember that all cases of recurrent DKA are preventable and it is up to you to avoid a subsequent episode.*

Case study

Case study 2.1

A 15-month-old boy was admitted to the hospital with drowsiness and decreased level of consciousness. The mother reported that he had had very heavy nappies during the last weeks and had a large quantity of urine output when he was sleeping, so she initially thought that the nappies she was using were of bad quality and had changed brands several times during the previous weeks. She initially reported this to her pediatrician, who suggested she should diminish the quantity of milk and water she was offering to her child during the day and at night. She reported, however, that the child was crying and was very agitated unless he received milk or water almost every hour.

On admission, he had diminished skin turgor, prolonged capillary refill time, and his eyes were closed. He had no verbal response and was not responding to painful stimuli. He had a bitter odor and deep sighing respiration. He weighed 10.3 kg (22.7 lb), although the mother reported a body weight of 12.0 kg (26.5 lb) at his last visit to the pediatrician. Pulse rate was 134/minute.

What is your diagnosis?

According to the history the child has had polyuria and polydipsia, so a form of diabetes is the most probable diagnosis. The diminished skin turgor and the prolonged capillary refill time are suggestive of significant dehydration. The deep sighing respiration is suggestive of metabolic acidosis and the bitter odor is most probably due to ketone production. Therefore, it cannot be diabetes insipidus, which could lead to dehydration but not to metabolic acidosis or ketone production. The most probable diagnosis is therefore diabetic ketoacidosis.

Which laboratory investigations will you initiate?

Since the most probable diagnosis is diabetic ketoacidosis, capillary blood glucose should immediately be determined to establish the diagnosis and blood should be taken for determination of blood glucose, urea nitrogen, creatinine, sodium, potassium, phosphate, chloride, complete blood count, and blood gases for pH and bicarbonate determination. Since the child is not responding and severely

dehydrated a urinary catheter should be introduced to obtain urine for ketone determination and document urine output.

Where should the child be managed?

Because of his diminished level of consciousness and very young age the child should be managed in an intensive care unit with expertise in management of children with diabetic ketoacidosis.

What are the first steps in the child's management?

An IV route for resuscitation should be introduced and normal saline infusion (NaCl 0.9%) at a rate of 20ml/kg body weight should be administered in the first hour. A second IV route should be placed for insulin administration that should be started after the first hour of fluid administration and a third IV route should be placed, if possible, at a distant site from the routes used for fluid and insulin administration, for frequent blood sampling.

How do you calculate the total amount of fluids that should be administered?

Since the child is very dehydrated, we estimate a 10% fluid deficit and calculate the amount of fluid that has to be administered during the following 48 hours, dividing it evenly over the 48 hours. The fluid that has to be administered in these 48 hours is the sum of fluid losses due to dehydration plus the amount of maintenance fluid for the 48 hours. Thus:

Total fluid to be administered
 = losses + (2 × daily maintenance volume).

Since the initial 20ml/kg of fluid that was given during the first hour were administered for resuscitation, this amount will not be subtracted from the total amount of fluid to be given in the subsequent hours.

The initial laboratory examinations reveal a blood glucose level of 870mg/dl (48.3mmol/L), sodium of 129mEq/L, potassium of 3.2mEq/L, serum urea nitrogen of 62mg/dl, hematocrit of 42%, arterial pH 7.02, bicarbonate 3mmol/L, and base excess of -22.

How would you comment on these laboratory results?

- The child had severe diabetic ketoacidosis, since arterial pH was <7.1 and bicarbonate concentration <5mmol/L.

- The documented hyponatremia was factitious, due to the very high blood glucose level. The corrected sodium concentration should be calculated according to the formula:

corrected sodium concentration

$$= \text{measured Na} + 2([\text{plasma glucose in mmol/L} - 5.6]/5.6)$$

where 1 mmol/L of glucose corresponds to 18 mg/dl.

In this case it is therefore:

$$\text{corrected Na} = 129 \text{ (mEq/L)} + 2 \times (48.3 - 5.6/5.6) = 144.25 \text{ mEq/L}$$

- The high urea nitrogen and hematocrit levels are due to significant hypertonic dehydration.
- Although serum potassium is not very low, there is a significant potassium deficit that will be aggravated as soon as the insulin infusion is started. Therefore, potassium supplementation of the fluid administered should be started immediately. The starting potassium concentration in the infusate should be 40 mmol/L and subsequently corrected according to serum potassium levels.

How often should you monitor your patient?

Clinical vital signs (arterial blood pressure, pulses, respiratory rate) and neurological status should be documented every hour, as well as blood glucose and arterial gases, until improvement is documented.

Serum sodium, potassium, chloride, urea, and phosphate should initially be measured every hour and subsequently every 2 hours upon stabilization.

Insulin and fluid infusion should also be monitored every hour and be documented on a flowchart, where all laboratory results are also documented.

How much insulin should you provide?

Since insulin is administered not only to restore euglycemia, but mainly to treat metabolic acidosis, insulin should be provided IV after the first hour of fluid administration at a dose of 0.1 IU/kg per hour, with close monitoring of blood glucose in order to avoid rapid lowering due to the very young age of the patient. It may also be wise to start with 0.05 IU/kg per hour of insulin due to the very young age of the patient and re-evaluate according to the fall in blood glucose. If blood glucose falls steeply before resolution of diabetic ketoacidosis, consider adding more glucose to the fluids

administered since insulin is needed to counter acidosis, which normally takes longer than achievement of euglycemia.

What is your main concern in such a child?

The most severe complication of diabetic ketoacidosis, especially in very young children, is cerebral edema and every effort should be made to avoid this life-threatening severe complication.

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CHAPTER 3

Hyperosmolar non-ketotic hyperglycemia

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Definition

Hyperosmolar non-ketotic hyperglycemia (also called hyperosmolar hyperglycemic state [HHS]) is one of the most serious acute complications of diabetes, with significant morbidity and mortality. Together with diabetic ketoacidosis (DKA) it represents an extreme in the spectrum of hyperglycemic states, and in fact significant overlap between these two conditions has been reported in more than one third of cases.¹

HHS is characterized by usually extreme hyperglycemia (serum glucose >600 mg/dl [33.3 mmol/L]), hyperosmolality, and profound dehydration, without significant ketoacidosis.² The essential difference from DKA is that in HHS there is little or no ketoacid accumulation (most patients with HHS have an admission pH > 7.30 , a serum bicarbonate >18 mEq/L, and test negative for ketones in serum and urine, although mild ketonemia may be present); the serum glucose concentration is usually much higher (frequently exceeding 1000 mg/dl [56 mmol/L]); the plasma osmolality is high (it may reach 380 mOsm/kg); and neurological abnormalities are frequently present (including coma in 25–50% of cases). The definitions proposed by the American Diabetes Association for DKA and HHS are shown in Table 1.1.^{1,3}

Diabetic Emergencies: Diagnosis and Clinical Management, First Edition. Nikolaos Katsilambros, Christina Kanaka-Gantenbein, Stavros Liatis, Konstantinos Makrilakis, Nikolaos Tentolouris.

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Summary box

HHS is usually characterized by:

- extreme hyperglycemia (serum glucose >600 mg/dl [33.3 mmol/L])
- hyperosmolality (serum osmolality >320 mOsm/kg H₂O)
- profound dehydration
- lack of significant ketoacidosis

Epidemiology

HHS is most commonly seen in older individuals (>65 years of age) with Type 2 diabetes.⁴ The incidence of HHS is difficult to determine because of the lack of population-based studies and the multiple combined illnesses often found in these patients. In general, it is estimated that the rate of hospital admissions due to HHS is lower than the rate due to DKA and accounts for <1% of all primary diabetic admissions.⁵ The mortality attributed to HHS is higher than that of DKA, with rates ranging from 5% to 20%; as in DKA, mortality is most often due to the underlying precipitating illness. The prognosis is substantially worsened at the extremes of age and in the presence of coma, hypotension, and severe co-morbidities.¹⁻⁷

Potential causes

The commonest factors that predispose to HHS are not much different than those in DKA. HHS most frequently occurs in older patients with Type 2 diabetes mellitus who have some concomitant illness that leads to reduced fluid intake. Infection (usually of the respiratory or the urinary tract) is the most frequent cause, but many other conditions can lead to altered mentation, dehydration, or both. Such precipitating factors include discontinuation of or inadequate insulin therapy, pancreatitis, myocardial infarction, cerebrovascular accident, endocrine disorders, and drugs (Box 3.1).¹ The fact also that these patients have either impaired physical activity and/or reduced thirst drive due to their older age contributes to their propensity for dehydration. In some instances the concomitant illness may not be identifiable.

Summary box

HHS most frequently occurs in older patients with Type 2 diabetes mellitus who have some concomitant illness that leads to reduced fluid intake

Box 3.1 Predisposing or precipitating factors for HHS**Inadequate insulin treatment or non-compliance (21–41%)****Acute illness**

- Infection (32–60%)
 - Pneumonia
 - Urinary tract infection
 - Sepsis
- Cerebrovascular accident
- Myocardial infarction
- Acute pancreatitis
- Acute pulmonary embolus
- Intestinal obstruction
- Dialysis, peritoneal
- Mesenteric thrombosis
- Renal failure
- Heat stroke
- Hypothermia
- Subdural hematoma
- Severe burns

Endocrine

- Acromegaly
- Thyrotoxicosis
- Cushing's syndrome

Drugs/therapy

- Beta-adrenergic blockers
- Calcium-channel blockers
- Chlorpromazine

Continued

Box 3.1 (*Continued*)

- Chlorthalidone
- Cimetidine
- Clozapine
- Diazoxide
- Ethacrynic acid
- Immunosuppressive agents
- L-asparaginase
- Loxapine
- Olanzapine
- Phenytoin
- Propranolol
- Steroids
- Thiazide diuretics
- Total parenteral nutrition

Previously undiagnosed diabetes

The basic mechanism underlying both DKA and HHS is a reduction in the net effective action of insulin, with concomitant elevation of counter-regulatory hormones, primarily glucagon, but also catecholamines, cortisol, and growth hormone. In patients with a pre-existing lack of or resistance to insulin, a physiological stress such as an acute illness can cause further net reduction in circulating insulin. Decreased renal clearance and decreased peripheral utilization of glucose lead to hyperglycemia. Hyperglycemia and hyperosmolality result in an osmotic diuresis and an osmotic shift of fluid from the intracellular to the intravascular space, resulting in further intracellular dehydration. The increased diuresis also leads to loss of electrolytes such as sodium and potassium.⁸ Figure 1.1 depicts the basic pathophysiological mechanisms leading to HHS and DKA.³

Unlike patients with DKA, those with HHS do not develop significant ketoacidosis, but the reason for this is not completely understood. Contributing factors likely include the availability of insulin in amounts sufficient to inhibit ketogenesis (by inhibiting lipolysis in adipose tissue) but not sufficient to prevent hyperglycemia (the available insulin is not able to suppress gluconeogenesis and glycogenolysis in the liver). Additionally, hyperosmolality itself

may decrease lipolysis, limiting the amount of free fatty acids available for ketogenesis. Also, lower levels of counter-regulatory hormones have been found in patients with HHS compared to those with DKA.⁹

Patients with HHS also usually exhibit much higher hyperglycemia than those with DKA. Two factors are responsible for this effect:

- People with HHS usually present late in the course of their disease because they lack the early symptoms of ketoacidosis (shortness of breath, abdominal pain) and thus have more long-standing deterioration of their illness, with signs of mental compromise due to hyperosmolality.
- The second reason is that people with HHS are older, with more compromised renal function, and thus have a lower capacity to excrete glucose in the urine compared to persons with DKA. Older people also have other physical limitations to seek water intake or have diminished thirst drive, which accentuate their dehydration potential and their propensity to hyperosmolality.¹⁰

Diagnosis

The earliest symptoms of marked hyperglycemia are polyuria, polydipsia, and weight loss. Unlike DKA, which usually evolves rapidly over a 24-hour period, symptoms in HHS develop more insidiously, often persisting for several days or even weeks before people seek medical attention and require hospital admission. As the degree or duration of hyperglycemia progresses, neurological symptoms, including lethargy, focal signs, and obtundation, which can progress to coma in later stages, can be seen. Neurological symptoms are most common in HHS (because of higher degrees of dehydration and hyperosmolality—or because of a cerebrovascular accident that precipitated the hyperglycemic crisis), while hyperventilation and abdominal pain are primarily limited to patients with DKA.¹

Summary box

Decreased mental state is the commonest reason why people with HHS are brought to the hospital

The clinical picture is related to the degree of dehydration and hypovolemia, the degree of hyperosmolality, and the precipitating factor that led to HHS. Polyuria, polydipsia, and weight loss are the usual prodromal symptoms. Due to hypovolemia, patients exhibit impaired peripheral circulation, tachycardia, hypotension, and cold extremities. Mental status may vary from slight confusion/obundation to coma. Serum osmolality has been shown to correlate significantly with mental status, both in DKA and HHS, and is the most important determinant of mental status.⁷ The severity of hyperosmolality can be evaluated by calculating effective serum osmolality (normal values: 285 ± 5), using the formula⁷:

$$\text{Effective osmolality (mOsm/kg)} = 2 \times [\text{measured serum Na}^+ \text{ (mEq/L)}] + \text{glucose (mg/dl)}/18$$

In the calculation of effective serum osmolality, the urea concentration is not taken into account because urea is freely permeable and its accumulation does not induce major changes in intracellular (including brain) volume or the osmotic gradient across the cell membrane.

Total serum osmolality (normal values: 290 ± 5) is calculated by the formula:

$$\text{Total osmolality (mOsm/kg)} = 2 \times [\text{measured serum Na}^+ \text{ (mEq/L)}] + \text{glucose (mg/dl)}/18 + \text{BUN (mg/dl)}/2.8$$

Neurological deterioration primarily occurs in patients with an effective serum osmolality >320 – 330 mOsm/kg. If the patient's mental status is out of proportion to the effective osmolality, another etiology for impaired mental status should be sought. The rise in serum osmolality is only in part due to the rise in serum glucose. The increase in serum osmolality pulls water out of the cells, which tends to reduce the serum osmolality toward normal and lower the serum sodium. The marked hyperosmolality seen in HHS is primarily due to the glucose-induced osmotic diuresis that causes water loss in excess of sodium and potassium. This is the reason why patients with end-stage renal disease (who do not produce any urine) can develop severe hyperglycemia, with serum glucose concentrations that can exceed 1000–1500 mg/dl (56–83 mmol/L), but because there is little or no osmotic diuresis the rise in serum osmolality is limited, hyponatremia is present, and they develop few or no neurological symptoms.¹¹

Summary box

The presence of stupor or coma in a diabetic patient with an effective plasma osmolality $<320\text{ mOsm/kg}$ demands immediate consideration of other causes of the mental status change

Because HHS is a medical emergency that requires prompt recognition and management, an initial history and rapid but careful physical examination should focus on airway, breathing, and circulation (ABC), mental status, possible precipitating events (e.g., source of infection, myocardial infarction, etc.), and volume status. These steps should allow determination of the degree of urgency and priority with which various laboratory results should be obtained, so that treatment can start without delay.

Physical examination reveals signs of volume depletion, including decreased skin turgor, dry axillae and oral mucosa, low jugular venous pressure, and, if severe, hypotension. The neurological findings noted above (confusion/obtundation, coma) also may be seen, or even focal neurological signs such as convulsions, motor or sensory deficits, delirium, or chorea. Fever is rare, even in the presence of infection, because of peripheral vasoconstriction due to the hypovolemia.

The easiest and most urgent laboratory tests after a prompt history and physical examination are determination of blood glucose by finger-stick and urinalysis with reagent strips to assess qualitative amounts of glucose, ketones, nitrite, and leukocyte esterase in the urine.

The initial laboratory evaluation of a patient with suspected DKA or HHS should include:

- Serum glucose
- Serum electrolytes (with calculation of the anion gap), blood urea nitrogen (BUN), and plasma creatinine
- Complete blood count with differential
- Urinalysis and urine ketones by dipstick
- Plasma osmolality
- Serum ketones (if urine ketones are present)
- Arterial blood gas if the serum bicarbonate is substantially reduced
- Electrocardiogram.

Additional testing, such as cultures of urine, sputum, and blood, serum lipase and amylase, and chest X-ray or X-ray of other organs (foot, etc.), should be performed on an individual basis.

Laboratory findings are dominated by signs of uncontrolled diabetes and dehydration. Plasma glucose concentrations are particularly high ($>1000\text{ mg/dl}$ [56 mmol/L] in two thirds of cases) and usually range between 800 and 2400 mg/dl ($44\text{--}133\text{ mmol/L}$).² Renal function is often impaired, with elevated BUN and creatinine levels. Even acute renal failure may sometimes ensue, the main cause of which is usually the rhabdomyolysis attributed to hypophosphatemia and prolonged muscle compression in a comatose patient. Hemoglobin and hematocrit may be increased (due to hemoconcentration) and liver function tests may be abnormal (due to fatty infiltration of the liver). The majority of patients present with leukocytosis due to the stress of the underlying condition that led to HHS (as a result of hypercortisolemia and increased catecholamine secretion). However, a white blood cell count $>25,000/\mu\text{L}$ or a band count $>10\%$ may indicate infection and a need for further work-up.

The serum sodium concentration may vary, as factors are present that can both lower or raise it. The final serum sodium concentration will reflect the balance between dilution of sodium due to osmotic water movement out of the cells, and concentration of sodium due to glucosuria-induced osmotic diuresis, resulting in water loss in excess of sodium. The admission serum sodium is usually low because of the osmotic flux of water from the intracellular to the extracellular space in the presence of hyperglycemia. An increased or even normal serum sodium concentration in the presence of hyperglycemia indicates a rather profound degree of free water loss (from the urine or occasionally also due to gastrointestinal losses). To assess the severity of sodium and water deficit, serum sodium may be corrected by adding 1.6 mEq/L to the measured serum sodium for each 100 mg/dl of glucose above 100 mg/dl .¹²

Patients at presentation have a potassium deficit that averages $3\text{--}5\text{ mg/kg}$. A number of factors contribute to this deficit, particularly increased urinary losses due both to the glucose osmotic diuresis and to the need to maintain electroneutrality as ketoacid anions are excreted. Gastrointestinal losses and the loss of potassium from the cells due to glycogenolysis and proteolysis also

may play a contributory role. Despite these potassium losses, the serum potassium concentration is usually normal or, in one third of patients, elevated on admission. It is thought that hyperosmolality and insulin deficiency are primarily responsible for the relative rise in the serum potassium concentration in this setting. The rise in plasma osmolality leads to osmotic water movement out of the cells. This can promote the parallel movement of potassium into the extracellular fluid. Also, since insulin normally promotes potassium uptake by the cells, insulin deficiency contributes to elevated serum potassium levels. Patients with low-normal or low serum potassium concentration on admission have severe total-body potassium deficiency and require careful cardiac monitoring and more vigorous potassium replacement because treatment lowers potassium further and can provoke cardiac dysrhythmia.¹³

Patients with uncontrolled hyperglycemia are typically in negative phosphate balance because of decreased phosphate intake and phosphaturia caused by osmotic diuresis.^{9,14} Despite phosphate depletion, the serum phosphate concentration at presentation is usually normal or even high, because both insulin deficiency and metabolic acidosis cause a shift of phosphate out of the cells.

Table 1.2 provides estimates of the typical water and electrolyte deficits in DKA and HHS.

Occasionally, marked hyperlipidemia and lactescent serum are observed, due to the marked hyperglycemia.

By definition, patients with HHS have no or only mild ketonemia and ketonuria. However, approximately 50% of patients may have an elevated anion gap acidosis because of concomitant ketoacidosis or lactic acidosis.

Clinical management

The management of HHS is similar to that of DKA (see Chapters 1 and 2). It includes correction of the fluid and electrolyte abnormalities that are typically present and administration of insulin.^{1,3,15} Therapy should also aim at simultaneous identification and treatment of the precipitating factors that led to the hyperglycemic decompensation (Box 3.1). Frequent monitoring of the patient is essential (Table 1.3). Protocols for the management of HHS are summarized in Figure 3.1.¹

Summary box

Management of HHS includes:

- Treatment of dehydration and restoration of intravascular volume
- Gradual decrease of hyperglycemia and hyperosmolality
- Correction of electrolyte disturbances
- Identification and treatment of precipitating events

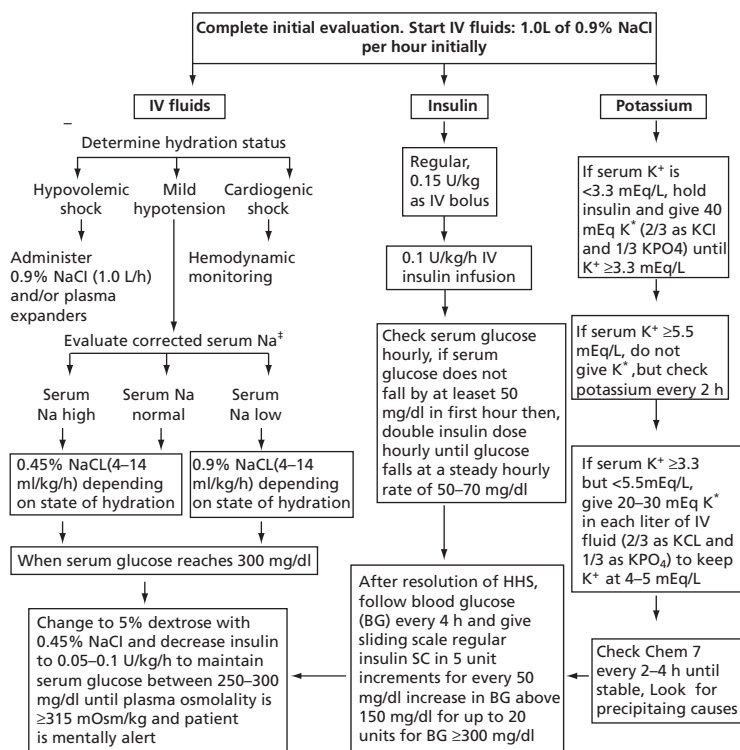


Figure 3.1 General protocol for the management of adult patients with HHS. Adapted from: Kitabchi AE, et al. *Diabetes Care* 2001; 24: 131–153 (with permission).

The serum glucose should initially be measured every hour until stable, while serum electrolytes, BUN, creatinine, and arterial (or venous) pH should be measured every 2–4 hours, depending on disease severity and the clinical response.^{1,3} Effective serum osmolality can be calculated as analyzed above.

Fluid therapy

Initial fluid therapy is directed toward expansion of the intravascular, interstitial, and intracellular volume—all of which are reduced in HHS—and restoration of renal perfusion. The typical total body water and electrolyte deficits are shown in Table 1.2. The aim of therapy is to replete the extracellular fluid volume without inducing cerebral edema due to too rapid a reduction in the plasma osmolality.

In patients with hypovolemic shock, 0.9% normal saline should be infused as quickly as possible. Otherwise, as long as there is no cardiac failure, isotonic saline (0.9% NaCl) is infused at a rate of 15–20 ml/kg per hour (usually 1.0–1.5 L during the first hour). This solution will replace the fluid deficit, correct the extracellular volume depletion more rapidly than one-half isotonic saline, lower the plasma osmolality (since it is still hypo-osmotic to the patient), and reduce the serum glucose concentration, both by dilution and by increasing urinary glucose excretion as renal perfusion is increased. The subsequent choice for fluid replacement depends upon the state of hydration, serum electrolyte levels, and urinary output. If corrected serum Na^+ is low, infusion of normal saline is continued at a rate of 4–14 ml/kg per hour for a few more hours. If corrected serum Na^+ is normal or high, one-half isotonic saline (0.45% normal saline) at a rate of 4–14 ml/kg per hour is initiated, depending on the state of hydration (to replace the free water loss induced by the glucose osmotic diuresis). Potassium supplementation (often necessary to replete the K^+ deficit) will also affect the osmolality of the infused fluid because K^+ is as osmotically active as Na^+ and thus the addition of K^+ to isotonic saline results in the generation of a hypertonic fluid that will not decrease the serum hyperosmolality. Thus, half-normal saline is indicated in this situation.¹⁶

The progress of successful fluid and electrolyte replacement is judged by frequent monitoring of hemodynamics (improvement in blood pressure), laboratory evaluation, fluid intake/output, and clinical examination. Fluid replacement should correct the estimated deficits within the first 24 hours. In patients with renal or cardiac compromise, more frequent monitoring must be performed during fluid resuscitation to avoid iatrogenic pulmonary edema.

Summary box

Fluid replacement should correct the estimated deficits within the first 24 hours

When blood glucose concentration reaches ~ 300 mg/dl (16.7 mmol/L), fluid infusion is switched to 5% dextrose to allow continued insulin administration at a decreased rate (see below) while at the same time avoiding hypoglycemia. Some authors¹ prefer to infuse a mixture of 5% dextrose with 0.45% NaCl, instead of 5% dextrose alone. This should continue until plasma osmolality is close to 315 mOsm/kg and the patient is mentally alert.

Insulin therapy

As in DKA, insulin therapy is essential in HHS (together with aggressive fluid hydration) to lower plasma glucose concentration (it primarily acts by decreasing hepatic glucose production rather than enhancing peripheral utilization). The route and the dose of insulin administration have been the subject of many studies in the past. It has been shown that any route of administration (intravenous, intramuscular, or subcutaneous) is ultimately effective, but the intravenous route is preferred because of concerns about decreased absorption with intramuscular or subcutaneous injections (at least initially) in dehydrated patients with vasoconstriction. The administration of continuous intravenous infusion of regular insulin is the preferred route also because of its short half-life and easy titration. Regarding dose, low doses of insulin have been shown to be as effective as high doses, with much less risk of hypoglycemia.^{17,18}

Insulin resistance is present in most patients with Type 2 diabetes. During HHS there are additional confounding factors such as stress (elevated counter-regulatory hormones), free fatty acids (FFAs), hemoconcentration, electrolyte deficiencies, ketone bodies, and particularly hyperosmolality that exaggerate the insulin resistance state. However, replacement of fluid and electrolytes alone may diminish this insulin resistance by decreasing levels of counter-regulatory hormones and hyperglycemia as well as by decreasing osmolality, making the cells more responsive to insulin. Low-dose insulin therapy is therefore most effective when preceded or accompanied by initial fluid and electrolyte replacement. Thus, after an initial infusion of isotonic saline to increase insulin responsiveness by lowering the plasma osmolality, the only indication for delaying insulin therapy is a serum potassium < 3.3 mEq/L, since insulin will worsen the hypokalemia by driving potassium into the cells (see below).

Summary box

Low-dose insulin therapy is most effective when preceded or accompanied by initial fluid and electrolyte replacement

Intravenous regular insulin infusion

An initial regular insulin bolus of 0.1 IU per kg of body weight (i.e., 8 units in an 80 kg person) is given intravenously, followed by a continuous infusion of 0.1 IU/kg per hour (i.e., 8 units per hour in an 80 kg person). The purpose of the initial bolus is to more rapidly activate insulin receptors.¹⁹ However, a recent randomized trial (in DKA patients) showed that a bolus dose was not necessary if intravenous insulin was infused at a rate of 0.14 IU/kg per hour (i.e., 11 units per hour in an 80 kg person).²⁰

An easy way to construct the insulin infusate is to mix 50 IU of regular insulin with 500 ml of 0.9% NaCl, thus creating a solution with a concentration of 1 IU insulin for every 10 ml solution and then infusing at the desired rate (for example 80 ml/h if 8 IU/h are needed).

The low dose of regular insulin usually decreases the serum glucose concentration by 50–70 mg/dl (2.8–3.9 mmol/L) per hour or more.^{19,21} Higher insulin doses do not generally produce a more prominent hypoglycemic effect, possibly because the insulin receptors are already saturated. If the serum glucose level does not fall by 50–70 mg/dl (2.8–3.9 mmol/L) from the initial value in the first hour, the insulin infusion rate should be doubled every hour until a steady decline in serum glucose is achieved. If serum glucose levels fail to fall, the intravenous access should be checked to make certain that the insulin is being delivered and that no filters are interposed that may bind insulin. The rate of fall in serum glucose may be more pronounced in patients with HHS (rather than with DKA) because the former are typically more volume depleted and aggressive rehydration has a more pronounced effect on their glucose levels. More rapid falls in glucose levels (more than 50–70 mg/dl [2.8–3.9 mmol/L] per hour) should be avoided to reduce the risk of cerebral edema.

As mentioned above, when the serum glucose concentration reaches 250–300 mg/dl (13.9–16.7 mmol/L), the intravenous saline solution is switched to 5% dextrose in saline, and it may be possible

to decrease the insulin infusion rate to 0.02–0.05 IU/kg per hour (i.e. 1.6–4.0 units per hour in an 80 kg person). This will decrease the risk of cerebral edema.

Other routes of insulin administration

If intravenous insulin infusion is not possible (due to either lack of intravenous access or local technical problems), intramuscular (IM) or subcutaneous (SC) administration is equally effective, albeit maybe at a more delayed pace.¹⁷ Most studies have evaluated IM or SC insulin administration in DKA patients (rather than HHS ones) but the results are expected to be similar.²² Intravenous administration has been shown to produce a more rapid fall in plasma glucose (and ketone bodies) in the first two hours, when compared with regular insulin used in the sc injections. Thereafter, there were no significant differences in the rate of decline of plasma glucose or ketones, or in the time required for glucose to reach 250–300 mg/dl (13.9–16.7 mmol/L) or for complete recovery from diabetic decompensation.

Potassium supplementation

Patients with HHS usually have a high total-body K^+ deficit (Table 1.2) at presentation, due mainly to renal but also to gastrointestinal losses during the development of hyperglycemic decompensation. The increase in renal potassium excretion is primarily related to the glucose osmotic diuresis and to hypovolemia-induced hyperaldosteronism. Despite the total-body potassium deficit, the serum K^+ concentration is usually normal or, in some cases, elevated at presentation, due primarily to insulin deficiency and hyperosmolality, both of which result in potassium shift out of the cells. This change in K^+ distribution is rapidly reversed with the administration of insulin, resulting in an often dramatic fall in the serum K^+ concentration. As a result, careful monitoring of serum K^+ is an essential part of the management of HHS.²³

If initial serum K^+ concentration is >5.3 mEq/L, no extra K^+ is added to the infused fluids. In patients with serum K^+ concentration <5.3 mEq/L, potassium chloride (20–30 mEq in each L) is generally added to the replacement fluid to prevent hypokalemia, assuming an adequate urine output (>50 ml/h). If the patient is hemodynamically stable, one-half isotonic saline is preferred, since the addition of potassium to isotonic saline will result in a hypertonic solution that will delay correction of the serum hyperosmolality. The goal

of K^+ supplementation is to maintain the serum potassium level between 4.0 and 5.0 mEq/L.^{1,3}

In patients who are hypokalemic at presentation (serum K^+ concentration <3.3 mEq/L), potassium repletion is more urgent. Such patients require aggressive potassium replacement (20–30 mEq/h), which usually requires 40–60 mEq/L added to one-half isotonic saline. Since insulin will worsen the hypokalemia, insulin therapy should be delayed until the serum potassium is >3.3 mEq/L to avoid possible arrhythmias, cardiac arrest, and respiratory muscle weakness.²⁴

Summary box

In patients with hypokalemia at presentation (serum K^+ concentration <3.3 mEq/L), insulin should be withheld until serum K^+ concentration is corrected

Phosphate supplementation

Despite a significant total-body phosphate deficit at presentation (Table 1.2), most patients have normal or elevated serum phosphate levels.¹⁴ As with potassium balance, phosphate depletion is revealed following the institution of insulin therapy, frequently leading to hypophosphatemia, which is usually asymptomatic. Clinically evident hemolysis and rhabdomyolysis with myoglobinuria are rare complications of hypophosphatemia.

No studies are available on the use of phosphate in the treatment of HHS. In DKA patients, however, prospective randomized studies have failed to show any benefit of phosphate supplementation on the clinical outcome, and overzealous phosphate administration can lead to hypocalcemia and hypomagnesemia.²⁵ However, to avoid potential cardiac and skeletal muscle weakness and respiratory depression due to hypophosphatemia, careful phosphate replacement may sometimes be indicated in patients with cardiac dysfunction, anemia, or respiratory depression and in those with serum phosphate concentration <1.0 mg/dl (0.32 mmol/L).²⁶ When needed, 20–30 mEq potassium phosphate can be added to each L of the replacement fluids. The maximal rate of phosphate replacement generally regarded as safe to treat severe hypophosphatemia is 4.5 mmol/h (1.5 ml/h of potassium phosphate).

Avoidance of complications

Hypoglycemia and hypokalemia are the two most common complications of treatment of hyperglycemic crises with insulin. They have both been reduced significantly, however, with the administration of low-dose insulin and careful monitoring and replacement of serum potassium.^{27,28} Frequent blood glucose monitoring (every 1–2 hours) is mandatory to recognize hypoglycemia because many patients with long-standing hyperglycemia who develop hypoglycemia during treatment do not experience adrenergic manifestations of sweating, nervousness, fatigue, hunger, and tachycardia.

Another complication is hyperglycemia, which may result from abrupt interruption of intravenous insulin without prior coverage with subcutaneous insulin. This too has been decreased with careful adherence to treatment protocols.³

Two of the most serious complications of hyperglycemic crises are the development of cerebral edema and thromboembolic complications. Cerebral edema most commonly develops in young children with DKA²⁹ and has very rarely been reported in adult patients with HHS. It is associated, however, with a high mortality rate (20–40%). Symptoms and signs are variable and include onset of headache, gradual deterioration in the level of consciousness, seizures, sphincter incontinence, papillary changes, papilledema, bradycardia, elevation in blood pressure, and respiratory arrest. Proposed mechanisms include the role of cerebral ischemia/hypoxia, the generation of various inflammatory mediators, increased cerebral blood flow, disruption of cell membrane ion transport, and a rapid shift in extracellular and intracellular fluids, resulting in changes in osmolality. Prevention might include avoidance of excessive hydration and rapid reduction of plasma osmolality, a gradual decrease in serum glucose, and maintenance of serum glucose between 250 and 300 mg/dl (13.9–16.7 mmol/L) until the patient's serum osmolality is normalized and mental status is improved. Data evaluating the outcome and treatment of cerebral edema in adults are not available. Recommendations for treatment are based upon clinical judgment in the absence of scientific evidence. Mannitol infusion (0.25–1.0 g/kg), hypertonic saline infusion (3% normal saline at a rate of 5–10 ml/kg over 30 min), and mechanical ventilation are suggested for treatment of cerebral edema.²⁹ These approaches raise the plasma osmolality, resulting in

osmotic movement of water out of the brain and a reduction in cerebral edema.³⁰

Summary box

- Gradual deterioration in the level of consciousness in a patient being treated for a hyperglycemic crisis should alert the physician to the possibility of cerebral edema
- Avoidance of excessive hydration and rapid reduction of plasma osmolality, a gradual decrease in serum glucose, and maintenance of serum glucose between 250 and 300 mg/dl (13.9–16.7 mmol/L) until the patient's serum osmolality is normalized and mental status is improved are recommended preventive measures for cerebral edema

HHS patients are also predisposed to thromboembolic complications due to their extreme dehydration status, diminished cardiac output, and increased blood viscosity owing to hyperosmolality. Increased platelet activation, plasminogen activator inhibitor (PAI)-1 activation, and endothelial dysfunction also contribute. The administration of prophylactic low-molecular-weight heparin subcutaneously is recommended by some, while others only treat clinically overt thromboembolic events as they occur.¹⁸

Rhabdomyolysis is another potential complication of HHS, possibly attributable to severe hyperosmolality.¹⁸ The diagnosis is suggested by a greatly elevated serum creatinine kinase (CK) concentration (usually >1000 IU/L) in the absence of alternative causes such as myocardial infarction, stroke, end-stage renal failure, or hypothyroidism. Aggressive hydration is needed to prevent renal damage from circulating myoglobin, but dialysis is sometimes required.

Follow-up management/care

Patients with HHS should be aggressively treated with intravenous fluids/electrolytes and insulin administration until the hyperglycemic crisis is resolved. Criteria for resolution of HHS include return of serum osmolality to levels <315 mOsm/kg, a normal mental status, and ability of the patient to eat.

Summary box

Criteria for resolution of HHS include:

- return of serum osmolality to levels $<315 \text{ mOsm/kg}$
- a normal mental status
- ability of the patient to eat

When this occurs, subcutaneous insulin therapy can be started. Insulin has a half-life of only 8–9 minutes. Thus, to prevent recurrence of hyperglycemia during the transition period to subcutaneous insulin, it is important to allow an overlap of 1–2 hours between discontinuation of intravenous insulin and the administration of subcutaneous insulin.³ If the patient is unable to take oral nutrition, it is preferable to continue the intravenous insulin infusion. Patients with known diabetes may be given insulin at the dosage they were receiving before, as long as it was controlling glucose properly and provided other acute stressful conditions (e.g., acute myocardial infarction, stroke) are not present. In insulin-naïve patients, a multi-dose insulin regimen should be started at a dose of 0.5–0.8 IU/kg per day, including bolus and basal insulin, until an optimal dose is established. Good clinical judgment and frequent glucose assessment are vital in initiating a new insulin regimen in insulin-naïve patients.

Following discharge from the hospital, insulin treatment is often recommended for the first 2–3 months.¹⁸ Many patients with HHS secrete sufficient endogenous insulin to be successfully treated in the long term with oral antidiabetic medicines. Pointers to insulin independence include excellent glycemic control (or recurrent hypoglycemia) with relatively small doses of insulin. Nevertheless, these features are not always reliable and the overall clinical and biochemical profile of the patient should be carefully evaluated before deciding not to use insulin.

Summary box

To prevent recurrence of hyperglycemia during the transition period to subcutaneous insulin, it is important to allow an overlap of 1–2 hours between discontinuation of intravenous insulin and the administration of subcutaneous insulin

Patient advice

HHS is a serious medical condition with a high mortality rate. The majority of affected patients are elderly, with impaired access to medical care, a diminished social network, and other intercurrent illnesses. Many cases can be prevented by proper patient education, better access to medical care, and effective communication of the patient with a health care provider during periods of intercurrent illness.

Proper advice to patients should include the following (see also Chapter 8):

- Never discontinue insulin during an acute illness and communicate with the health care provider as quickly as possible.
- Intensify home self-monitoring of blood glucose and initiate early treatment with short-acting insulin if needed.
- In cases of nausea/vomiting/diarrhea, drink plenty of fluids and avoid dehydration.

Education on sick-day rules is required for family members or caregivers for elderly or hospitalized patients in long-term facilities.

Case studies

Case study 3.1

An 82-year-old man with a 17-year history of Type 2 diabetes was brought by family members to the Emergency Room (ER) with fever, confusion, and an infected ulcer on the right little toe that had developed over the previous few days. He had been treated with metformin and glimepiride for the last 15 years, with inadequate diabetic control. He did not frequently check his blood sugar levels at home and his last HbA_{1c} was 10.2% around 1.5 years earlier. He had been advised to start insulin then, but had refused. Family members said he had been urinating a lot lately and was gradually getting fatigued and sleepy.

On physical examination in the ER, his blood pressure was 84/52 mmHg, pulse rate 112/min, and temperature 38.4°C (101.1°F). He was drowsy and disoriented to place and time. His oral mucosa was dry and skin turgor diminished. Laboratory evaluation revealed a serum glucose level of 1120 mg/dl (62.3 mmol/L), sodium 152 mEq/L, potassium 5.4 mEq/L, bicarbonate 20 mmol/L, urea 84 mg/dl (13.9 mmol/L), creatinine 1.9 mg/dl (168 µmol/L), normal arterial blood gases, and 1(+) ketones in the urine. His WBC count

was 18,000/ μ l (80% polymorphonuclears), hematocrit and platelet counts were normal, the C-reactive protein was 122 mg/L (normal <5), and erythrocyte sedimentation rate (ESR) 85 mm/h (normal 0–20).

What is your diagnosis and what should immediate care be?

The patient obviously has a hyperglycemic crisis with extremely high blood glucose levels and evidence of dehydration. He has no acidosis and minimal, if any, ketosis. His effective serum osmolality is calculated to be very high, at 366.3 mOsm/kg [$2(\text{Na}) + \text{glucose (mg/dl)}/18$]. Thus, he fulfills all the criteria for HHS, with dehydration and obtundation. His infected toe ulcer, on top of his chronically uncontrolled diabetes, is most likely the precipitating factor that led to this crisis. He should immediately be aggressively hydrated, started on insulin, and treated for his toe infection.

An ECG showed sinus tachycardia and no evidence of ischemia. A chest X-ray was normal and a right foot X-ray showed no evidence of osteomyelitis. Blood cultures and cultures from the foot ulcer area were obtained and IV antibiotics were started.

The patient was also started on IV fluids (he received 0.9% normal saline 1 L within 1 hour in the ER) and another 1 L was continued for the next 2 hours. At the same time he was started on IV regular insulin: he received an 8 IU IV bolus (his weight was estimated to be 80 kg) and a continuous IV infusion of 8 IU/h was initiated.

The patient was admitted to the hospital. His blood sugar levels were monitored by finger-stick every hour and by laboratory evaluation (together with the electrolytes) every 2 hours. One hour later, his finger-stick blood sugar level using a portable bedside glucose meter showed “HI”. The treating physician got worried that his condition was not improving appropriately and consulted a diabetes specialist. Was his worry justified?

The answer is that a bedside portable glucose meter is usually able to measure blood glucose levels up to 600 mg/dl (33.3 mmol/L). As this patient’s initial blood glucose level was 1120 mg/dl (62.3 mmol/L) and as an appropriate blood glucose decline should be 50–70 mg/dl (2.8–3.9 mmol/L) per hour, it is appropriate one hour after the

initiation of treatment for the blood sugar still to be $>600\text{mg/dl}$ (33.3mmol/L); thus it is not necessarily true that the condition is not improving appropriately. The physician should send a serum glucose level to the laboratory and judge the progress of the patient's condition by an exact plasma measurement.

Laboratory evaluation one hour later showed a plasma glucose level of 970mg/dl (53.9mmol/L), serum K^+ 4.1mEq/L , serum Na^+ 148mEq/L , phosphate 2.3mg/dl (0.74mmol/L), urea 48mg/dl (8.0mmol/L), and creatinine 1.3mg/dl ($114.9\mu\text{mol/L}$).

The blood glucose level is decreasing appropriately with treatment (by 150mg/dl [8.3mmol/L] in 2 hours). His IV fluids were continued at a rate of 500ml/h 0.9% normal saline, and 20mEq of potassium chloride were added to each L of fluids. Insulin infusion was continued at the same rate. Laboratory monitoring continued every 2 hours (see Table 1.3). His mental status and hemodynamics improved (blood pressure was raised to $112/74\text{mmHg}$).

Two hours later his blood glucose was 800mg/dl (44.4mmol/L), serum K^+ 4.5mEq/L , serum Na^+ 145mEq/L .

Since his hyperosmolality has improved (estimated now at 334.4mOsm/kg) but has not completely resolved (the goal was to gradually drop to $<315\text{mOsm/kg}$), his IV fluids were changed to 0.45% normal saline with continued K^+ supplementation, at an infusion rate of 250ml/h , and insulin administration was continued.

Six hours later his blood sugar was 290mg/dl (16.1mmol/L), serum K^+ 4.9mEq/L , serum Na^+ 138mEq/L .

His insulin infusion rate was decreased to 4IU/h and his IV fluids changed to 5% dextrose in water with 0.45% normal saline, infused at a rate of 250ml/h , with the goal of keeping the glucose level around $250\text{--}300\text{mg/dl}$ ($13.9\text{--}16.7\text{mmol/L}$).

Next morning the patient was alert and oriented. Blood pressure was normal, his blood sugar level was 240mg/dl (13.3mmol/L), and electrolytes were within normal limits. He was able to eat without nausea or vomiting.

He was given a subcutaneous injection of 10IU regular insulin and 10IU glargine insulin and the IV insulin infusion was stopped 1 hour later, to continue with blood glucose monitoring every 6 hours and glargine and regular insulin subcutaneously. His family members were educated regarding insulin administration techniques and doses. The patient was discharged from the hospital after 4 days, in stable condition, to continue with p.o. antibiotics and insulin at home. He was to follow up in the outpatient clinic in one week's time.

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CHAPTER 4

Hypoglycemia caused by insulin

Stavros Liatis, Nikolaos Katsilambros

Definition of hypoglycemia

Hypoglycemia is defined as blood glucose concentration below the normal range, the lower level of normality being equivocal. From a physiological point of view, a detectable impairment of higher cerebral function has been demonstrated at plasma glucose levels of 54 mg/dl (3 mmol/L) or less.¹ Counter-regulatory responses to hypoglycemia have been described at plasma levels between 65–70 mg/dl (3.6–3.9 mmol/L).²

Summary box

On clinical grounds, hypoglycemia is defined by its clinical presentation, characterized by the classical *triad of Whipple*, i.e., symptoms/signs compatible with low plasma glucose concentration, low plasma glucose measurement (usually between 65–70 mg/dL [3.6–3.9 mmol/L]), and resolution of symptoms after increase of blood glucose level

Physiology of blood glucose regulation

In normal individuals, blood glucose levels remain under strict regulation, coordinated by complex neuroendocrine mechanisms. This happens because glucose is an obligate metabolic fuel for the

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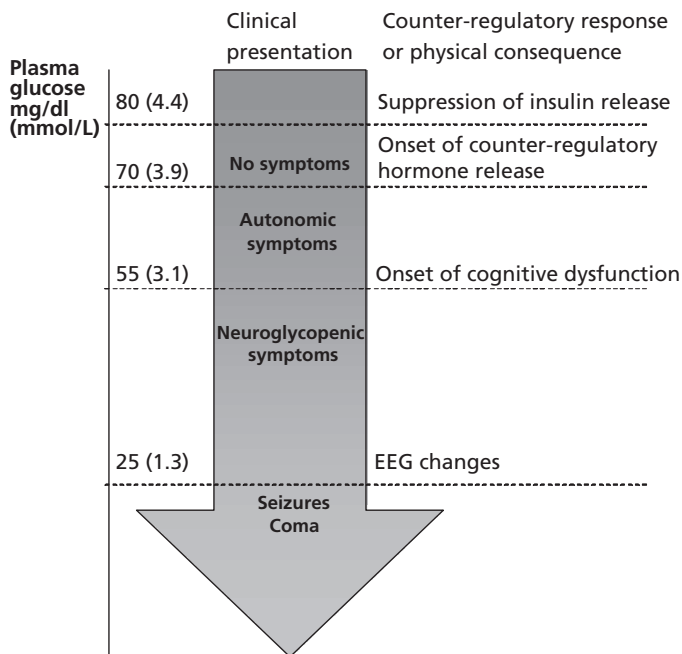


Figure 4.1 Normal counter-regulatory responses and clinical presentation of hypoglycaemia.

brain, which, due to its very limited fuel-storing capacity, is dependent on the continuous supply of glucose from the blood stream. Therefore, in cases where blood glucose falls, or tends to fall, below normal range, several counter-regulatory responses are elicited² (Figure 4.1). The key components of this counter-regulatory mechanism are:

1. Suppression of insulin secretion from the pancreatic β -cells. This happens even when plasma glucose is within the normal range, if there is a tendency for plasma glucose to decline (below 80 mg/dl [4.4 mmol/L]).
2. Increase in glucagon secretion from the pancreatic α -cells, when plasma glucose is in the range of 65–70 mg/dl (3.6–3.9 mmol/L).
3. Increase in adrenomedullary epinephrine secretion when plasma glucose falls below the normal range (65–70 mg/dl [3.6–3.9 mmol/L]).
4. Increased growth hormone and adrenocorticotropin secretion from the anterior pituitary.

This battery of neuroendocrine responses results in increased endogenous glucose production, reduction in peripheral glucose utilization, increased lipolysis, and increased proteolysis, all combining to “push” plasma glucose concentration to increase. It has to be emphasized, however, that insulin, glucagon, and epinephrine play the most critical role among the glucose counter-regulatory factors, acting within a few minutes.

The defense mechanism against falling blood glucose is so effective that hypoglycemia is a very uncommon condition in non-diabetic individuals.

Summary box

In patients with diabetes, both a non-suppressible insulin excess (due to exogenous insulin administration or increased endogenous insulin secretion induced by certain drugs) and a defective counter-regulatory response to hypoglycemia are the key factors explaining the frequent clinical phenomenon of hypoglycemic episodes in affected individuals

Hypoglycemia in diabetes

Pathophysiology of low blood glucose counter-regulation

Hypoglycemia in diabetes usually results as a consequence of treatment aimed at correction of hyperglycemia. Iatrogenic hypoglycemia is considered the major obstacle preventing good glycemic control in patients with diabetes. The problem appears when insulin deficiency, which is a hallmark of the disease, is overcorrected. Nevertheless, hypoglycemia is a much more common problem in Type 1 than in Type 2 diabetes, the first of which is characterized by absolute insulin deficiency, whereas the latter is characterized by relative deficiency which, however, deteriorates with time.

Hypoglycemic thresholds (i.e., the plasma glucose values at which counter-regulatory mechanisms are activated) may be altered in patients with diabetes, depending on glucose control. A higher threshold is often associated with poor glycemic control while, in tightly-controlled individuals or those with frequent episodes of hypoglycemia, a shift toward lower levels is often observed.^{3,4}

In Type 1 diabetes, complete lack of insulin secretion results in impairment of the first counter-regulatory defensive mechanism against hypoglycemia, that is, reduction of insulin secretion. In these patients, plasma insulin levels are directly related to the passive absorption of exogenously administered insulin and its pharmacokinetic profile. In addition, endogenous insulin deficiency is considered responsible for a blunted glucagon response to hypoglycemia. This is probably a signaling defect, since glucagon-secreting cells and secretion of glucagon induced by stimuli other than hypoglycemia are intact in such patients.⁵ Finally, even the epinephrine response to hypoglycemia is attenuated in Type 1 diabetes, mainly due to the shift of its counter-regulatory threshold toward lower plasma glucose levels.⁴ The latter is believed to be the result of frequent iatrogenic hypoglycemic events, although sleep, and to some extent prior exercise, may similarly influence epinephrine response.⁶

In patients with Type 2 diabetes, the counter-regulatory response has been reported to be relatively intact in the early stages of the disease but the frequency of iatrogenic hypoglycemia typically increases as the insulin deficiency progresses and insulin therapy is introduced. The potential effects of aging on counter-regulation should also be taken into account, as people with Type 2 diabetes are often elderly and are hence more susceptible to the clinical consequences of hypoglycemia. It has been reported that the magnitude of the counter-regulatory response is reduced in the elderly (≥ 65 years) when blood glucose falls below 60 mg/dl (3.3 mmol/L), while it is preserved at more profound hypoglycemic levels (blood glucose < 50 mg/dl [2.8 mmol/L]).⁷

Summary box

Hypoglycemia unawareness (often described as a “syndrome”) is defined as the inability of a person to recognize the presence of hypoglycemia and, hence, to promptly react in order to correct his or her blood glucose levels

Hypoglycemia unawareness is due to the attenuated epinephrine response observed in patients with diabetes and frequent hypoglycemic episodes. It has been shown that recent antecedent iatrogenic hypoglycemia leads to defective glucose counter-regulation and,

consequently, to hypoglycemia unawareness, which in turn predisposes to further episodes of iatrogenic hypoglycemia.⁸ This vicious circle has been recently described as hypoglycemia-associated autonomic failure (HAAF). That concept has been extended to include exercise- and sleep-related HAAF.⁶ HAAF is reversible, however, since it has been shown that the sympathoadrenal response to hypoglycemia is a dynamic process.⁹ Reversal of HAAF is mainly based on strict avoidance of low blood glucose levels over a period of 2–4 weeks.⁹

Summary box

Defective glucose counter-regulation can be improved by meticulous avoidance of iatrogenic hypoglycemia for 2–4 weeks

Classification of iatrogenic hypoglycemia

A confirmatory blood glucose test during an episode of hypoglycemia is often unavailable while, in other cases, a discrepancy may be observed between self-measured blood glucose values and clinical presentation of hypoglycemia (usually due to defective counter-regulation). These situations often create confusion both in clinical practice and in clinical studies. In 2005, an American Diabetes Association (ADA) workgroup on hypoglycemia proposed certain criteria to define and classify hypoglycemic events in patients with diabetes:¹⁰

- *Severe hypoglycemia*: any hypoglycemic episode that the patient is unable to self-treat, requiring the assistance of another person to deal with it. Subdivisions of this category are cases requiring medical assistance and those that lead to seizures or/and coma. A low blood glucose measurement is not necessary, as recovery attributable to the administration of carbohydrates (either orally or parenterally) and/or glucagon is considered sufficient evidence that the event was induced by a low blood glucose concentration.
- *Documented symptomatic hypoglycemia*: an event with typical symptoms of hypoglycemia, accompanied by a measured plasma glucose concentration ≤ 70 mg/dl (3.9 mmol/L).
- *Asymptomatic hypoglycemia*: an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose

concentration ≤ 70 mg/dl (3.9 mmol/L). It has been argued by some experts that defining hypoglycemia as any value ≤ 70 mg/dl (3.9 mmol/L) may lead to overestimation of clinically important events.¹¹ The European Agency for Evaluation of Medicinal Products (EMA) proposed a respective value of ≤ 54 mg/dl (3.0 mmol/L) when assessing the hypoglycemic risk of different treatment regimens, as this might have the advantage of better clinically detecting significant hypoglycemia.¹² This approach, however, could result to an underestimation of true hypoglycemic events.

- *Probable symptomatic hypoglycemia*: a self-reported event that is not confirmed by a measured low plasma glucose value. This is a common situation in patients who experience frequent hypoglycemic episodes and often neglect to measure their blood glucose, despite typical symptoms, choosing to directly consume carbohydrates in order to treat the event.
- *Relative hypoglycemia*: a situation “opposite” to the previous one. It refers to a symptomatic event interpreted by the patient as hypoglycemia but accompanied by a plasma glucose value higher than 70 mg/dl (3.9 mmol/L). This situation can be explained by the fact that when glycemic control is poor, symptoms of hypoglycemia may appear at higher plasma glucose levels.

Summary box

In clinical practice the most important discrimination lies between severe and mild hypoglycemia, the latter including all non-severe hypoglycemic events

The term “moderate hypoglycemia” is sometimes used to describe a self-treated event which, however, leads to significant “lifestyle disruption.” This category is falling out of use due to its unclear definition.

The frequency of iatrogenic hypoglycemia in diabetes

Iatrogenic hypoglycemia is a frequent medical condition associated with the treatment of patients with diabetes. It is more frequent by far in Type 1 than in Type 2 diabetes, although rates rise in Type 2

diabetes in direct relation to the duration of the disease and the severity of insulin deficiency. This can be explained by the fact that in these situations more aggressive therapies are introduced, including exogenous insulin administration.

Patients with Type 1 diabetes often become familiar with hypoglycemia as part of their everyday life. It has been estimated that in patients treated with intensive insulin therapy aimed at optimal glycemic control (recommended for all patients with Type 1 diabetes, since it has been shown to reduce long-term complications), plasma glucose levels may be less than 50–60 mg/dl (2.8–3.3 mmol/L) about 10% of the time.¹³ A JDRF (Juvenile Diabetes Research Foundation) study using continuous glucose monitoring in 176 intensively treated individuals with Type 1 diabetes showed that hypoglycemic events occurred during 8.5% of nights and the duration of hypoglycemia was ≥ 2 hours on 23% of nights with hypoglycemia.¹⁴ In the Diabetes Control and Complications Trial (DCCT), the reported rate of serious hypoglycemic events was 62 per 100 patient-years in the intensively treated arm, while even conventionally treated patients experienced more than one such episode during the 6.5-year duration of the trial.¹⁵ In unselected cohorts, the frequency of severe hypoglycemia ranged between 1.0 and 1.7 episodes per patient-year.¹⁶

In Type 2 diabetes, the frequency of hypoglycemia is highly variable due to the heterogeneity of the disease and its treatment modalities. Newly-diagnosed patients, or those in the primary stages of the disease who are being treated with diet alone or metformin monotherapy, rarely experience hypoglycemia. On the other hand, when severe insulin deficiency develops and insulin is used in variable treatment regimens, hypoglycemia can become a frequent side effect. In the landmark UKPDS (United Kingdom Prospective Diabetes Study) study, only the severe episodes were reported. As expected, a higher frequency of hypoglycemia was associated with advanced stages of the disease and with intensive, compared with conventional, treatment with either sulfonylureas or insulin.¹⁷ In the so-called “megatrials” of Type 2 diabetes (ACCORD, ADVANCE, and VADT^{18–20}), which examined the effects of very intensive management of hyperglycemia aiming at an HbA_{1c} <6.5%, the rates of severe hypoglycemia in the intensive arm of the trials were high but varied considerably: 3.2, 0.7, and 9.0 per 100 patient-years respectively. The lowest incidence of hypoglycemia was reported in the ADVANCE trial which had the lowest rate

of insulin use (40% at the end) compared to the other two trials (>75%).

It has to be emphasized, however, that data obtained in clinical trials are not usually representative of the general diabetic population, since participants receive treatment according to strict protocols while reporting of hypoglycemic episodes follows certain defined rules. On the other hand, most observational studies record the frequency of hypoglycemia retrospectively, relying on patient recall of low blood glucose episodes, a practice that is usually inaccurate. A population survey conducted in a region of Scotland (DARTS-MEMO database) recorded all episodes of severe hypoglycemia requiring emergency medical assistance and reported, over a 12-month period, that 7.3% of insulin-treated patients with Type 2 diabetes suffered at least one episode of severe hypoglycemia, a figure comparable to patients with Type 1 diabetes (7.1%).²¹ It has been shown, however, that people with insulin-treated Type 2 diabetes who exhibit a severe hypoglycemic episode may be more likely to require emergency assistance than people with Type 1 diabetes, since severe hypoglycemia in the latter group is often treated at home.²² In a 12-month survey of all attendances with a primary diagnosis of diabetes in two hospitals in the UK, 37% were due to hypoglycemia while hyperglycemia, the next most common reason for attendance, was affecting 14.9% of patients.²³

Summary box

Both mild and severe hypoglycemic episodes are much more common in Type 1 diabetes, while in Type 2 diabetes their frequency depends on the type of treatment and the degree of insulin deficiency, approaching, in some cases, that of Type 1 diabetes in intensively insulin-treated patients with advanced disease

Clinical presentation of hypoglycemia

Symptoms and signs of hypoglycemia (Table 4.1) are non-specific and vary considerably among patients with diabetes as their occurrence depends upon several factors such as degree of hypoglycemia, rapidity of glucose decline, age, level of activity, past experience of the patient, and presence of HAAF. The experience of a hypoglycemic event is somehow unique for a given patient, especially in patients with Type 1 diabetes. However, two main categories of

symptoms are clearly recognized: those elicited through the activation of the autonomic nervous system (mainly the sympathoadrenal system), which are usually described as “autonomic symptoms,” and those due to brain neuronal glucose deprivation, often described as “neuroglycopenic symptoms” (Table 4.1). Symptoms of hypoglycemia have also been categorized using factor analysis, a multivariate statistical technique that enables a large set of variables to be reduced to a smaller number of latent variables (or factors). This type of analysis has been used in several studies, both in non-diabetic individuals (using a hypoglycemic clamp experiment) and in people with insulin-treated diabetes, to classify the symptoms of acute hypoglycemia into groups.²⁴ A three-factor model (referred to as the Edinburgh Hypoglycemia Scale—Table 4.2) identified 11

Table 4.1 Symptoms and signs of hypoglycemia

Autonomic symptoms	Neuroglycopenic symptoms
Tremor	Weakness, fatigue
Sweating	Dizziness
Anxiety	Confusion
Nausea	Difficulty speaking
Palpitations	Inability to concentrate
Shivering	Drowsiness
Hunger	Sensation of warmth
Paresthesias	Behavioral changes
	Seizures
	Loss of consciousness
Autonomic signs	Neuroglycopenic signs
Pallor	Occasionally transient focal neurological deficits
Diaphoresis	
Tachycardia	
Mydriasis	
Increased systolic blood pressure	

Table 4.2 Classification of the 11 most common hypoglycemic symptoms by factor analysis (The Edinburgh Hypoglycemia Scale)²⁵

Autonomic	Neuroglycopenic	General malaise
Sweating	Confusion	Headache
Palpitations	Drowsiness	Nausea
Shaking	Odd behavior	
Hunger	Speech difficulty	
	Incoordination	

common symptoms and has been used subsequently by many researchers for the objective assessment of hypoglycemia.²⁵

Symptoms are elicited at different glucose concentrations, depending mainly upon the “quality” of glucose control.^{3, 4} Patients with poorly controlled diabetes and infrequent hypoglycemic events usually experience autonomic symptoms early, at plasma glucose concentrations even higher than those required to elicit symptoms in healthy individuals. On the other hand, patients with frequent hypoglycemic events (usually, but not exclusively, those with decent glycemic control) exhibit mild or no autonomic symptoms, since they often suffer from HAAF and hypoglycemia unawareness. In these patients, hypoglycemia commonly exhibits neuroglycopenic symptoms, typically elicited at lower plasma glucose concentrations, increasing the risk for severe hypoglycemic episodes.

Summary box

- Early recognition of hypoglycemia by the patient, irrespective of the specific symptoms elicited, is the key to successful self-management and avoidance of severe events, which can rarely even lead to death
- Hypoglycemia unawareness should be considered as a serious medical condition that requires specific management, especially since it can be reversed within a few weeks

Predisposing factors for hypoglycemia in insulin-treated patients

Iatrogenic hypoglycemia occurs when circulating insulin levels (depending mainly on the amount and the type of injected insulin)

exceed actual patient needs at the moment that hypoglycemia occurs. The most common causes of hypoglycemia in insulin-treated patients are a higher than required insulin dose, a missed/delayed meal, or increased, usually non-planned, physical activity.²⁶ Several other factors should be taken into account, however, in the evaluation of a hypoglycemic episode (Box 4.1). Special attention should be paid to identifying the glycemic threshold at which a particular patient recognizes hypoglycemia, since hypoglycemia unawareness is a strong predisposing factor for severe and recurrent

Box 4.1 Factors associated with the occurrence of severe hypoglycemia in insulin-treated patients

Insulin regimen

- Excessive insulin dose
 - Misjudgment (by patient or physician)
 - Mistake in preparation
 - Intentionally
- Time-related errors in insulin injection
- Wrong type of insulin used

Missed or delayed meal/snack

Increased physical activity

Nocturnal hypoglycemia

Hypoglycemia unawareness

Excessive alcohol consumption

Extremes of age

Withdrawal of glucocorticoids

Weight-loss dieting

Concomitant use of oral hypoglycemic medications (see Chapter 5)

Presence of co-morbidities

- Acute illness resulting in reduced food intake (e.g., gastroenteritis)
- Renal failure
- Hepatic failure
- Gastroparesis
- Adrenal insufficiency
- Dementia
- Psychiatric disease

hypoglycemic episodes. It is generally recommended that glycemic targets should be individualized and set after careful evaluation of each patient's history of hypoglycemic events (especially severe ones) and his/her potential risk for such serious episodes.²⁷ As a consequence, for elderly patients with co-morbidities (especially those with renal failure or cardiovascular disease) or patients with a low life expectancy, higher glycemic targets may be more appropriate.²⁷

Consequences of iatrogenic hypoglycemia

These can be divided into two main categories:

1. Consequences of acute hypoglycemia
2. Consequences of chronic recurrent hypoglycemia.

Consequences of acute hypoglycemia

Acute hypoglycemia can lead to health damage either directly (from deleterious effects of low blood glucose supply to the brain) or indirectly, usually via trauma due to loss of consciousness or seizures. As an example, hypoglycemia may occur during driving and may obviously cause road traffic accidents.

In the vast majority of cases, recovery from a severe hypoglycemic event, even if it manifests with seizures or coma, is complete. Sometimes, neurologic abnormalities can be observed immediately after recovery of consciousness and improve afterwards. Hypoglycemic hemiplegia is an uncommon condition that has been described as a hemiparetic state, presenting in the morning when the patient awakens after a nocturnal hypoglycemic event. The episode typically resolves after a few minutes or hours and may recur.²⁸ Permanent neurologic damage and death have been reported rarely,²⁹ especially after massive insulin overdose and delayed restoration of normoglycemia.³⁰

Another possible mechanism of acute health damage, including sudden death, due to hypoglycemia is via the induction of cardiovascular events. Hypoglycemia has been implicated in the so-called "dead-in-bed syndrome," the unexpected death of a young person with Type 1 diabetes found dead in an undisturbed bed.²⁹ It has also been suggested that the increased total mortality risk observed in the intensive glycemic control arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study might be due to the high rate of hypoglycemic events.¹⁸ However, this

insinuation has not been verified in post hoc analysis of the trial data.³¹

It has been shown that hypoglycemia, especially in patients with pre-existing cardiovascular disease, induces multiple proarrhythmic changes, mainly increasing pre-existent QT prolongation, producing intracellular Ca^{2+} overload, and decreasing serum K^+ .³² As a consequence, hypoglycemia is considered a state that may lead to sudden death (as a result of cardiac arrhythmia). Whereas the evidence supporting this view is strong from a basic science perspective, no large clinical studies have yet definitively confirmed it.³² Epidemiological confirmation of a causal association between hypoglycemia and arrhythmic events is difficult to prove due to the fact that firm postmortem evidence of hypoglycemia is virtually impossible to obtain. A recent extensive review of the possible link between hypoglycemia and ischemic cardiac events concluded that although small observational studies suggest an association between hypoglycemia and such events, there is currently no evidence for causality.³³

A severe hypoglycemic event is an annoying and unpleasant experience that can also be embarrassing from a social point of view. Hence, such an event may be associated with adverse psychological consequences including fear of hypoglycemia, high levels of anxiety, and deterioration of glycemic control.¹³

Consequences of chronic recurrent hypoglycemia

The existence of a link between recurrent severe hypoglycemic events and impaired cognitive function is an issue of debate. There is some evidence to suggest that severe hypoglycemia is associated with a decline of the intelligence quotient (IQ) in patients with Type 1 diabetes.³⁴ However, large, well-designed and controlled studies of the impact of recurrent hypoglycemia on cognitive performance in patients with diabetes are sparse and inconclusive. It has been shown prospectively (up to 18 years of follow-up) that intensified insulin therapy does not lead to cognitive impairment despite its association with a high rate of hypoglycemic events.³⁵ Interestingly, it has been recently shown in rats that recurrent moderate hypoglycemia preconditions the brain and protects neurons against damage induced by severe hypoglycemia.³⁶ The situation is probably different in the developing brain. In children with Type 1 diabetes, some aspects of attention are adversely affected by a history of seizures from hypoglycemia.³⁷

A longitudinal cohort study of nearly 17,000 patients with a mean age of 65 years and Type 2 diabetes indicated an association between severe hypoglycemic episodes and a higher risk of dementia.³⁸

Summary box

It is extremely important to avoid episodes of severe hypoglycemia in young children, in whom slightly higher glycemic targets might be more appropriate. Similarly, elderly patients might also be at increased risk of brain damage from recurrent episodes of hypoglycemia

Management of hypoglycemia caused by insulin treatment

Management includes the following steps:

- Restoration of normal plasma glucose levels
- Prevention of relapse in the short term
- Prevention of recurrent episodes in the long term.

Restoration of normal plasma glucose levels (Figure 4.2)

In non-severe hypoglycemia, the oral consumption of carbohydrates is usually adequate to restore plasma glucose levels above the lower limit of the normal range. Patients starting insulin for the treatment of their diabetes should be taught to recognize the symptoms of hypoglycemia and how to react in case of a hypoglycemic event. Self-monitoring blood glucose (SMBG) is strongly recommended for these patients.²⁷ If hypoglycemia is suspected, a blood glucose measurement using a portable glucose meter is recommended in order to confirm low plasma glucose, although this option is not always feasible. Therefore, in clinical practice, many mild hypoglycemic episodes are classified as “probable symptomatic hypoglycemia” (see Classification of hypoglycemia). On the other hand, patients with hypoglycemia unawareness typically discover mild hypoglycemia during routine self-monitoring. Such events are classified as “asymptomatic hypoglycemia” and should be treated as promptly as symptomatic ones.

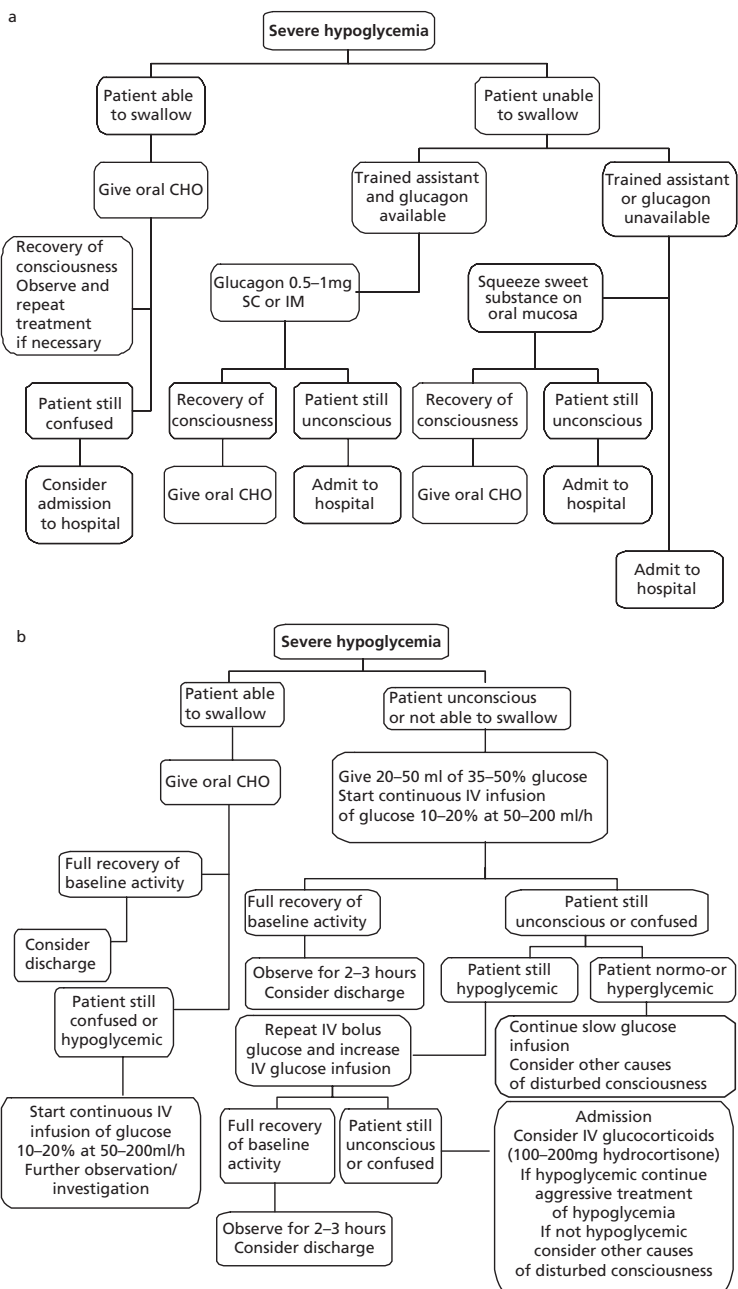


Figure 4.2 Management of severe iatrogenic hypoglycemia due to insulin: a. in the outpatient setting. b in the emergency setting. CHO, carbohydrate.

Summary box

It is mandatory that patients do not delay self-treatment of mild episodes, since they could rapidly evolve to severe life-threatening hypoglycemia

Rapidly-absorbed simple carbohydrates are preferred over complex ones, since the latter might fail to promptly correct blood glucose. Glucose tablets (usually provided as 5 g each) are effective and often preferred, especially by well-educated patients with Type 1 diabetes. Alternatively, glucose- or sucrose-containing beverages such as non-diet soft drinks or sweetened fruit juice are also quite effective and usually readily available.³⁹ In patients being treated with insulin in combination with an α -glucosidase inhibitor (acarbose or miglitol), pure glucose-containing tablets or beverages are prescribed, since these drugs delay the degradation of disaccharides (such as sucrose and fructose).

Summary box

Severe hypoglycemia is a potentially life-threatening condition and should be treated immediately

Severe hypoglycemia is defined as hypoglycemia that is not possible to self-manage (see Classification of hypoglycemia). If a patient is able to receive oral carbohydrates with the help of a third person, then this method constitutes the preferred way to correct low plasma glucose. The same rules as for mild episodes can be followed, although higher amounts of simple carbohydrates should likely be administered (40–50 g instead of 20 g). In comatose patients or those who are severely confused or refusing to collaborate, parenteral therapy is recommended. This can be administered either as glucagon injection or intravenous glucose solution.

Summary box

Glucagon is preferred when the hypoglycemic episode occurs during everyday activity and a third person (family member, close friend, roommate, school personnel, child care provider, etc.) has been educated to recognize such an event and act appropriately

If a glucose meter is available, blood glucose measurement is highly recommended in order to confirm low plasma glucose levels. Glucagon 1 mg should then be administered intramuscularly or subcutaneously. The glucagon kit should be readily available and the patient's relatives or friends should know how to mix the glucagon powder with the diluent, draw it from the vial, and give the injection. Some glucagon kits contain a syringe prefilled with the diluent, which is then inserted into the vial, mixed with the glucagon powder, and redrawn in the same syringe. Successful glucagon therapy requires that the glucagon kit be readily accessed and that the rescuer remain calm while properly preparing and administering the injection. If a glucose meter is not available, glucagon should still be given to the unconscious patient. Although coma might be due to marked hyperglycemia (with or without ketoacidosis) rather than hypoglycemia, the latter will be corrected, whereas no particularly deleterious effect will be produced if blood glucose concentration is high. It should be noted that hyperglycemic coma occurs progressively, usually over several hours or even days. In contrast, hypoglycemia evolves within a few minutes. In addition, in contrast to marked hyperglycemia, in hypoglycemia the skin is wet, deep tendon reflexes are increased, and there is mydriasis.

Recovery of consciousness and restoration of normal plasma glucose levels are expected in about 10–15 minutes. At this time the patient may have nausea or vomiting, a common side effect of glucagon administration. These symptoms, however, if present, last only a few minutes.

If a glucagon injection is not available (and there is no access to intravenous glucose), is there any other option for the unconscious hypoglycemic patient while awaiting emergency personnel? Some experts recommend family members or friends to squeeze and rub a sucrose-containing substance (such as white sugar, honey, syrup, or glucose gel) between the teeth and buccal mucosa, while keeping the patient's head tilted to the side. No data exist to support or reject this. Nevertheless, if such an instruction is given to patients' relatives, attention should be paid to avoid aspiration, which might have more deleterious consequences than hypoglycemia itself.

If there is no response to glucagon, intravenous glucose should be administered. Since glucagon acts by stimulating glycogenolysis, its administration may not be effective in case of heavy alcohol consumption, prolonged fasting, or hepatic failure. In addition, because glucagon stimulates insulin secretion as well, its administration may be less useful in Type 2 diabetes.¹³

Summary box

In the medical emergency setting, severe hypoglycemia should be treated by intravenous glucose infusion

No specific guidelines, based on the results of clinical trials, exist regarding the optimal way to treat severe hypoglycemia at the emergency room. Some experts recommend the intravenous administration of 20–50 ml of 50% glucose solution as a bolus, providing 10–25 g of glucose.^{13,40} Others suggest that a higher amount (75–200 ml) of a more dilute glucose solution (10–20%) should be preferred, given that the 50% solution might be tissue-toxic if extravasated.³⁰ We usually administer 50 ml of a 35% glucose solution, providing 17.5 g of glucose, as a bolus. This is sufficient to restore plasma glucose and lead to recovery of consciousness in the vast majority of cases. We have never observed any severe tissue necrosis due to extravasation.

According to some recommendations, bolus glucose administration should be followed by continuous infusion of a 10–20% glucose solution at a rate of 50–200 ml/h, depending on the degree of hypoglycemia and the patient's response to treatment. Plasma glucose should be re-measured 10–15 minutes after the initial glucose administration and a bolus infusion repeated if hypoglycemia persists. If plasma glucose has been restored but consciousness is still disturbed, the glucose infusion should be continued at a slow rate. Although other causes of impairment of consciousness should be considered, clinicians should be aware that occasionally full recovery of brain function might take several minutes or even hours. In rare cases of sustained neurological manifestations solely attributed to hypoglycemia, some experts recommend the administration of dexamethasone.⁴⁰

Prevention of relapse in the short term

Restoration of plasma glucose levels after an acute hypoglycemic event usually follows quickly after the administration of carbohydrates, either orally or intravenously, or after a glucagon injection. It is very important, however, to keep in mind that hypoglycemia tends to relapse in some cases, this tendency depending on the etiology of the initial decline in plasma glucose (Box 4.1).

Summary box

Follow-up after immediate plasma glucose correction is a cornerstone in the overall management of any hypoglycemic episode

In mild self-treated hypoglycemia, patients are advised to re-measure their plasma glucose levels 15 minutes after carbohydrate ingestion and repeat treatment in case of relapse or tendency towards relapse. If the next meal is scheduled more than one hour later, it is wise to consume a small amount of complex carbohydrates (e.g. a sandwich or a couple of pieces of fruit) in order to avoid recurrence of hypoglycemia.

In severe hypoglycemia treated with glucagon, it is recommended that immediately after regaining consciousness patients should receive oral carbohydrates providing 20–40 g of glucose in order to restore hepatic glycogen and prevent relapse of hypoglycemia. We advise patients recovering from severe hypoglycemia treated with glucagon to monitor their plasma glucose frequently (every half an hour) for the next few hours.

In severe hypoglycemia treated at the emergency room, a continuous infusion of a 10–20% glucose solution is generally recommended after the initial administration of bolus glucose, accompanied by frequent monitoring of capillary blood glucose. The decision on whether and when the patient should be discharged depends on response to treatment as well as on factors related to the cause of the hypoglycemic event, the age of the patient, and the presence of co-morbidities (Box 4.1).

Identification of the cause of the severe hypoglycemic event is crucial. As stated above, iatrogenic hypoglycemia occurs when circulating insulin exceeds actual patient needs, while, at the same time, counter-regulatory mechanisms fail to prevent the decline of blood glucose levels. The most common causes of hypoglycemia in insulin-treated patients are misjudgment of insulin dose, a missed/delayed meal, or increased, usually unplanned, physical activity. Other factors that should be taken into account in the evaluation of a severe hypoglycemic episode are listed in Box 4.1. In a 12-month survey of all attendances with hypoglycemia at the emergency department at two district general hospitals in the UK, only 11% of patients were admitted to hospital, 83% of patients were discharged, and 6% self-discharged.²³ Four out of the 10 admitted

patients had co-morbidities, 4 had a decreased Glasgow coma scale, 2 were above 80 years old, one had alcohol intoxication, and one was homeless. In another retrospective study from the UK, of 54 patients admitted to the hospital with a primary diagnosis of hypoglycemia, 9 had a relapse during the first 24 hours of hospitalization. The mortality rate was 7.4% (4 deaths) but only one was attributable to hypoglycemia itself, in a 63-year-old patient suffering from several co-morbidities.⁴¹

Summary box

Insulin-treated patients with iatrogenic hypoglycemia can be safely discharged from the emergency department if their level of functioning has returned to baseline, they are able to eat, their plasma glucose levels are constantly above 100 mg/dl (5.6 mmol/L) for at least 1 hour after discontinuation of glucose infusion, and no major co-morbidities are present

As an extra precaution, some experts recommend that patients at extremes of age should be observed for 24 hours. Patients who receive oral antidiabetic drugs in combination with insulin might also require further observation (see Chapter 5). Every case, however, should be carefully examined as criteria for admission are individualized.

Prevention of recurrent episodes in the long term

Recurrent hypoglycemia requires a thorough evaluation of diabetes management and should be an indication for referral to a diabetologist/endocrinologist. The circumstances before and during hypoglycemia, as well as the factors listed in Box 4.1, should be carefully examined in order to prevent further severe hypoglycemic episodes. Special consideration should be paid to diagnose the presence of HAAF and hypoglycemia unawareness, since these two conditions are significant risk factors for severe hypoglycemia. A careful history is usually adequate to identify hypoglycemia unawareness. In other cases, careful follow-up with frequent SMBG or even the use of a glucose sensor for continuous subcutaneous glucose monitoring may be recommended. The evaluation of patients with recurrent hypoglycemia and the management of hypoglycemia unawareness are beyond the scope of this book

and the reader is referred to recent extensive reviews on these topics.^{8,42}

Case studies

Case 4.1

A 65-year-old man with history of Type 2 diabetes presented to the emergency department at 10.30 pm. He claimed he had mistakenly injected himself about half an hour earlier with 75 IU of insulin lispro, a rapid-acting insulin analog, instead of insulin glargine, a long-acting insulin analog. The patient had had Type 2 diabetes for 17 years and had been receiving basal insulin (glargine) for the last 3 years. Four months earlier, due to his poor glycemic control, prandial insulin (lispro) was introduced at a dosage of 8 units before each meal, and was gradually increased to 12 IU. His glargine dosage was 75 IU every evening at bedtime. One month earlier his HbA_{1c} was 7.3%.

The patient reported a myocardial infarction eight years ago and a history of hypertension for the last 20 years. As well as insulin, he was taking low-dose aspirin, atorvastatin, carvedilol, ramipril, hydrochlorothiazide, amlodipine, and metformin.

The patient had realized his mistake only a few minutes after injection. He subsequently measured his capillary blood glucose and found it to be 132 mg/dl (7.3 mmol/L). He decided to “eat something sweet” and consumed 350 ml of sweetened fruit juice and one bar of dark chocolate, but he was still “too afraid” and decided to contact the nearest hospital. He arrived at the emergency room driving his own car.

Upon arrival, his capillary blood glucose was 91 mg/dl (6.7 mmol/L). He felt well, although “quite scared”. His vital signs were normal except for a mild sinus tachycardia (102 beats/min). His self-reported weight was 92 kg and his height 1.72 m (BMI 31.1 kg/m²).

How should this patient be managed?

This patient is in great danger of serious hypoglycemia. Despite his plasma glucose levels being still within the normal range, it could be estimated that the very high dose of rapid-acting insulin he had injected by mistake had just started to be absorbed at the injection site. Insulin lispro has a time-action profile similar to the other two rapid-acting insulin analogs available in most European countries

and the United States (aspart and glulisine). Its onset of action is 20–30 minutes after subcutaneous injection, the peak is at 90–120 minutes, and its action lasts 3–4 hours. As with any type of insulin, however, action duration is strongly positively related to the injected dose. There is actually one case reported in the literature of an attempted suicide with 300IU of insulin lispro injected subcutaneously, which resulted in protracted severe hypoglycemia for more than 11 hours.⁴³

The patient was admitted to the hospital due to impending severe hypoglycemia. Serum potassium at admission was 4.2 mEq/L. A continuous infusion of 20% glucose solution was immediately initiated at a rate of 100 ml/h, providing 20 g of glucose per hour. A mixed meal, rich in carbohydrates, was also administered to the patient. Capillary blood glucose was closely monitored (every 30 minutes). One hour after admission capillary blood glucose was 75 mg/dl (4.2 mmol/L). Glucose infusion was increased to 150 ml/h. At 01:30 am (about 3 hours after admission), a plasma glucose value of 48 mg/dl (2.7 mmol/L) was measured and 50 ml of 35% glucose solution were administered (providing 17.5 g of glucose) as a bolus IV and the 20% glucose infusion rate was increased to 200 ml/h. Serum potassium was 3.7 mEq/L and potassium chloride was added to the glucose infusion. During the rest of the night, plasma glucose values ranged between 95 and 155 mg/dl (5.3–8.6 mmol/L) with a mild tendency to increase over time. At 07:00 am (10 hours after the wrong insulin injection), capillary blood glucose was 181 mg/dl (10 mmol/L). The infusion rate was decreased to 100 ml/h and the patient was given his breakfast. One hour after breakfast, plasma glucose was 235 mg/dl (13.05 mmol/L) and the glucose infusion was stopped. The patient was further observed for 3 hours and then discharged, since he exhibited no further signs of blood glucose decline. He was instructed to continue his typical insulin program and inject insulin glargine at 10:00 pm. He was advised to keep different insulins in different places (e.g., prandial insulin in the kitchen and basal insulin in the bedroom). His diabetologist was contacted and informed about his hospitalization.

Comment

Mistakes in insulin administration are not rare in clinical practice and involve errors in prescription, interpretation of prescriptions, preparation, and injection technique. Patients on basal-bolus

therapy use two types of insulin, usually one or two injections of basal insulin (long-acting) and multiple injections of prandial insulin (short-acting). Meticulous education of the insulin-treated patient is mandatory for the success of every insulin regimen, especially for a basal-bolus scheme. Confusing short- with long-acting insulins might be extremely dangerous (as shown in this and other cases⁴⁴) and although insulin manufacturers fabricate vials and pens using different colors, depending on the type of insulin, special attention should be always paid.

Case 4.2

A 28-year-old male was admitted at the emergency room at 4.00 am after a hypoglycemic event, having failed to recover despite the administration of glucagon. The patient was accompanied by his wife who described that one hour before admission she had realized that her husband had fallen unconscious during his night's sleep. The patient had been diagnosed with Type 1 diabetes two years earlier. No other health problems were reported. His insulin regimen included NPH insulin injected twice a day (24IU in the morning and 18IU at bedtime) and regular insulin injected before each meal. He had had frequent episodes of hypoglycemia, especially during the last 2 weeks, when he started exercising at a gym. Nevertheless, he had not been brought to the hospital on any previous occasion. His wife was often the first one to notice him becoming hypoglycemic, as he would often become aggressive and exhibit signs of bizarre attitude. The patient had suffered from another episode of complete loss of consciousness one week earlier, but he had responded promptly after his wife administered 1 mg of glucagon injection subcutaneously. During the current episode his first capillary blood glucose, as measured by his wife, was "low" as indicated by the portable meter, which was not able to read a glucose level lower than 25 mg/dl (1.4 mmol/L). The patient did not respond to a glucagon injection (1 mg) that his wife had administered to him. She subsequently repeated the dose and a few minutes later he showed some signs of regaining consciousness but then vomited twice. His blood sugar was measured at that time to be 26 mg/dl (1.4 mmol/L) but he was too confused and aggressive to accept any food. The evening before this event occurred, he had injected his usual 18IU of insulin NPH at 11.00 pm. He and his wife had had a light dinner but also consumed a whole bottle of red wine. His wife reported that she "only had one or two glasses" out of the whole

bottle, while the rest was consumed by her husband. His wife insisted, however, that her husband was not a regular heavy drinker.

At the emergency room the patient was confused, disorientated, and very negative toward any intervention. His capillary blood glucose was 30 mg/dl (1.7 mmol/L). The department's staff managed to calm him down and he immediately responded to the administration of 50 ml 35% glucose solution given as an intravenous bolus infusion. He had nausea but did not vomit. A 10% continuous glucose infusion was started at a rate of 100 ml/h. Fifteen minutes later his capillary blood glucose was 121 mg/dl (6.7 mmol/L) and he was able to eat a sandwich and drink some orange juice. One hour after admission his capillary blood glucose was 249 mg/dl (13.8 mmol/L).

After his recovery the patient reported that the afternoon before the event had occurred he exercised "really hard" but his capillary blood glucose was normal after exercise and before dinner. He remembered feeling "quite dizzy" before falling asleep but thought this was probably due to the wine. He did not measure his blood glucose at that time.

Comment

This patient became a high risk for severe hypoglycemia that evening. Heavy exercise increases hypoglycemic risk, not only during or immediately following exercise, but several hours later as well, due to depletion of liver and muscle glycogen and the subsequent demand of these tissues for glucose to restore these pools. Furthermore, heavy alcohol consumption inhibits gluconeogenesis, further predisposing to, or even causing, hypoglycemia. The behavior-altering effects of alcohol can also cloud the recognition of hypoglycemia by the patient and those around him (family, colleagues, etc.), leading to delays in prompt treatment.

The combination of vigorous exercise with heavy alcohol consumption may lead to dramatic effects in insulin-treated patients if insulin dose is not reduced and frequent glucose monitoring is not performed. An additional danger derives from the fact that glucagon may be less effective in reversing hypoglycemia in the absence of adequate glycogen stores. In the case presented, inadequate response to glucagon was probably caused by incomplete replenishment of glycogen stores after exercise due to alcohol consumption.

It should also be noted that the use of NPH insulin as a substitute for basal insulin has been associated with increased risk of hypoglycemia 4–6 hours after its subcutaneous injection, corresponding to the peak of action of this insulin preparation. The use of basal insulin analogs (glargine and detemir) has been associated with a small but significant, in clinical trial terms, reduction of nocturnal hypoglycemia in patients with Type 1 diabetes, compared to insulin NPH.⁴⁵

Most importantly, this patient has hypoglycemia unawareness. Both previous episodes of hypoglycemia and sleep are associated with hypoglycemia-associated autonomic failure, a condition leading to unawareness of hypoglycemic episodes. Since HAAF substantially increases the risk of severe hypoglycemia, it is mandatory to reconsider the insulin plan for this patient in order to strictly avoid low blood glucose values in the next 15–20 days and consequently restore autonomic symptoms elicited by hypoglycemic glucose levels.

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CHAPTER 5

Hypoglycemia caused by insulin secretagogues

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Insulin secretagogues

Sulfonylureas and non-sulfonylurea insulin secretagogues (meglitinides) exert their antidiabetic effects by binding to the sulfonylurea receptor (SUR) on the β -cell, which regulates the activity of an ATP-dependent potassium channel.¹ Binding of insulin secretagogues to the SUR results in closure of the potassium channels and depolarization of the membrane of the β -cells, with subsequent opening of the calcium channels and stimulation of insulin release.¹ In the β -cell, insulin secretagogues increase insulin secretion in a relatively glucose-dependent fashion, resulting in a reduction of both fasting and postprandial glucose levels. The net effect is a reduction in HbA_{1c} of 1–2%, the exception being nateglinide, which is associated with a 0.5–1.0% reduction as a result of its short half-life and residence time on the SUR.²

Some characteristics of the insulin secretagogues currently available in many countries are shown in Table 5.1.

The first-generation sulfonylureas (tolbutamide, tolazamide, and chlorpropamide) bind significantly to plasma proteins and have high milligram dosage requirements. Because of the protein binding, they can displace or be displaced by other agents, leading to certain drug interactions. Tolbutamide is rapidly cleared by the liver and must be taken two to three times daily.^{3,4}

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Table 5.1 Characteristics of sulfonylureas and meglitinides

Generic name	Total daily dose range (mg)	Frequency of administration	Half-life (h)	Duration of action (h)	Metabolism
<i>First generation</i>					
Tolbutamide	500–2000	3 times daily	4.5–6.5	6–12	Mainly hepatic, <20% excreted unchanged in urine
Chlorpropamide	125–500	Once daily	36	60	Mainly renal, ~20% hepatic
Tolazamide	100–1000	Twice daily	7	12–24	Renal, hepatic
<i>Second generation</i>					
Glibenclamide (glyburide)	1.25–20*	2 or 3 times daily	Biphasic (4 and 10 h)	12–24	Hepatic (=100%); metabolites excreted in bile (50%) and urine (50%)
Glipizide	2.5–40	Twice daily	2–4	12–24	Hepatic; <10% excreted unchanged in urine
Glipizide extended release	2.5–20	Once daily	>12	24	Hepatic; <10% excreted unchanged in urine
Gliclazide	40–320	Twice daily	10–12	12–16	Hepatic; <5% excreted unchanged in urine
Gliclazide modified release (MR)	30–120	Once daily	12–20	24	Hepatic; <5% excreted unchanged in urine
<i>Third generation</i>					
Glimepiride	1–8 *	Once daily	5–8	16–24	Hepatic; inactive metabolites excreted in urine (60%) and feces (40%)
<i>Meglitinides</i>					
Repaglinide	0.5–16	3–4 times daily	1	2–6	Hepatic
Nateglinide	60–540	3 times daily	0.5–1.9	2–6	Hepatic; excreted in urine

*In Europe the maximum recommended daily dose of glibenclamide (glyburide) is 15mg and of glimepiride 6mg.

Chlorpropamide is slowly cleared by the kidney and accumulates, particularly when renal function declines, and as a result may cause serious hypoglycemia. Chlorpropamide also may cause an Antabuse (disulfiram)-like intolerance to alcohol, or potentiate antidiuretic hormone action leading to water intoxication. Because of these limitations, use of these first-generation agents is uncommon.^{3,4}

The second- and third-generation sulfonylureas (glibenclamide [glyburide], glipizide, and glimepiride) have lower total dosage requirements. They are metabolized mainly by the liver and cleared by the kidneys, except that glimepiride is excreted by both renal and hepatic mechanisms. Glibenclamide (glyburide) has an active metabolite that is excreted by the kidney. Thus, in the setting of renal insufficiency, glibenclamide (glyburide) is associated with greater concern and glimepiride with the least issues from a drug metabolism perspective. Both glibenclamide (glyburide) and glipizide require twice-daily dosage to produce 24-hour coverage. Glipizide and gliclazide are also available in extended-release formulations that, like glimepiride, are effective given once a day.^{3,4}

The newest non-sulfonylurea insulin secretagogues are meglitinides. Their action is mediated through the SUR, and they hold some structural homology to the sulfonylureas but do not contain the actual sulfonylurea moiety. Both repaglinide and nateglinide are rapidly absorbed after oral administration and rapidly cleared by hepatic metabolism. This rapid time-course—calls for two or three doses daily with meals. Repaglinide is able to reduce fasting levels of glucose despite its short half-life because of prolonged residence on the SUR complex and thus it is able to reduce HbA_{1c} equivalently to sulfonylureas. Nateglinide on the other hand has a short residence time and does not substantially reduce fasting glucose. As a result, nateglinide is the secretagogue with the most specific activity in lowering postprandial glucose and the lowest risk of hypoglycemia. However, because of its lack of effect on fasting glucose, its efficacy in lowering HbA_{1c} is modest.²⁻⁴

The main complication of insulin secretagogues is hypoglycemia. Risk factors for hypoglycemia are aging, past history of cardiovascular disease or stroke, impaired renal function, and reduced food intake (Box 5.1). The risk of hypoglycemia is also related to the pharmacological half-life of the medication and to the time it is bound to the SUR. Glibenclamide (glyburide) seems to be associated with the highest risk of hypoglycemia, followed by glimepiride, gliclazide, repaglinide, nateglinide, and sustained release formulations

of glipizide. The risk of severe hypoglycemia is low with meglitinides. Patients with modest hyperglycemia should be started with the lowest possible dose in order to avoid hypoglycemia. In addition, certain drug interactions can potentiate the hypoglycemic effects of insulin secretagogues (Box 5.2). The use of multiple medications can also affect appetite and further potentiate hypoglycemia.⁵

Box 5.1 Risk factors for hypoglycemia in patients treated with insulin secretagogues

- Aging
- Previous history of cardiovascular disease or stroke
- Impaired renal function
- Reduced food intake
- Use of sulfonylureas with long duration of action
- Polypharmacy

Box 5.2 Drug interactions

Drugs that may potentiate the hypoglycemic effect of glibenclamide (glyburide), glipizide, and glimepiride

- Non-steroidal anti-inflammatory agents
- Salicylates
- Sulfonamides
- Chloramphenicol
- Ciprofloxacin
- Trimethoprim
- Alcohol
- Fibrates
- Probenecid
- Allopurinol
- Coumarin derivatives
- Monoamine oxidase inhibitors
- β -adrenergic blockers

Drugs that may potentiate the hypoglycemic effect of gliclazide

- Non-steroidal anti-inflammatory agents
- Salicylates

Box 5.2 (*Continued*)

- Sulphonamides
- Tetracycline compounds
- Chloramphenicol
- Miconazole (oral forms)
- Coumarin derivatives
- Monoamine oxidase inhibitors
- Clofibrate
- Disopyramide
- Cimetidine
- β -adrenergic blockers

Drugs that may potentiate the hypoglycemic effect of repaglinide

- Non-steroidal anti-inflammatory agents
- Salicylates
- Sulphonamides
- Erythromycin
- Clarithromycin
- Trimethoprim
- Chloramphenicol
- Antifungals
- Coumarin derivatives
- Monoamine oxidase inhibitors
- Probenecid
- Gemfibrozil
- Ciclosporin (cyclosporine)
- Octreotide
- Alcohol
- Anabolic steroids
- Angiotensin-converting enzyme inhibitors
- β -adrenergic blockers

Drugs that may potentiate the hypoglycemic effect of nateglinide

- Angiotensin-converting enzyme inhibitors
- Antifungals
- Sulfapyrazone
- Gemfibrozil

Regarding drug interactions, antibiotics such as chloramphenicol, sulfonamides and ciprofloxacin, cimetidine, coumarin derivatives, and monoamine oxidase inhibitors may decrease hepatic metabolism of insulin secretagogues. Allopurinol, probenecid, and salicylates can decrease renal excretion of the medications and their metabolites. Fibrates, trimethoprim, salicylates, sulfonamides, and coumarin derivatives can displace sulfonylureas from albumin binding sites and increase their bioavailability. Antifungals may increase their plasma concentration. Alcohol inhibits gluconeogenesis and increases the risk of hypoglycemia.⁵

Summary box

- Sulfonylureas are classified according to their duration of action into short- and long-acting
- Long-acting, first- and second-generation sulfonylureas are more likely to cause hypoglycemia
- Meglitinides can cause mild or moderate hypoglycemia in the postprandial period but not severe hypoglycemia
- Insulin secretagogues may interact with many medications commonly used by patients with diabetes
- Risk factors for hypoglycemia caused by sulfonylureas include aging, previous history of cardiovascular disease or stroke, impaired renal function, reduced food intake, and concomitant treatments

Prevalence of hypoglycemia caused by insulin secretagogues

Data from the United Kingdom Prospective Diabetes Study have shown that over 10 years the frequency of all hypoglycemic episodes with glibenclamide (glyburide) was 17.0% and with chlorpropamide 11.0%; the frequency of severe hypoglycemia with glibenclamide (glyburide) was 0.6% and with chlorpropamide 0.4%. In the same study, the frequency of hypoglycemia with insulin was 36.5% and that of severe hypoglycemia 2.3% (Figure 5.1).⁶

A retrospective study in England showed a prevalence of 20% of hypoglycemia in patients treated with sulfonylurea (alone or in combination with metformin) within a period of 6 months.⁷ A Swedish study reported 19 cases of glipizide-associated severe hypoglycemia over a 7-year period. Eleven cases presented with coma, 3 cases with reduced consciousness, and 5 with other symptoms. It is of note

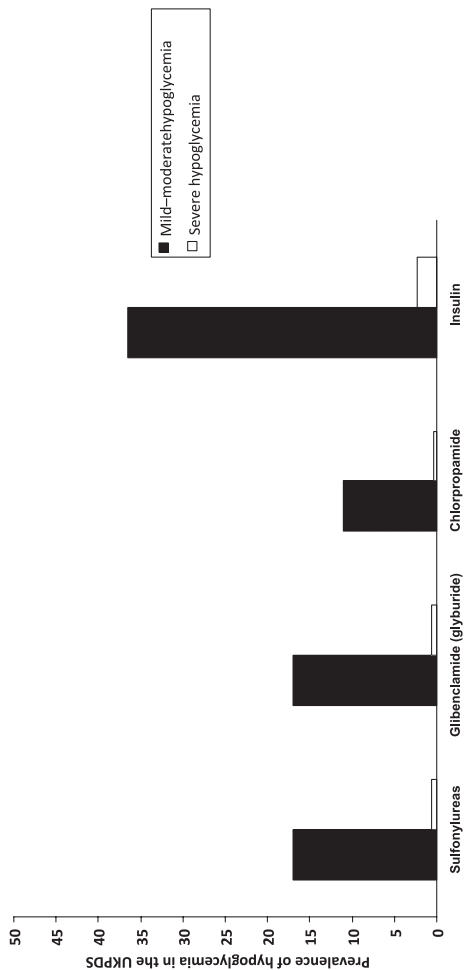


Figure 5.1 Prevalence of hypoglycemia in the UKPDS.

that 5 patients had prolonged or recurrent hypoglycemia for up to 60 hours, while 2 patients died.⁸ Another study from Switzerland showed that over 12 years the incidence of severe hypoglycemia was 0.224 episodes per 100 patient-years with long-acting sulfonylureas versus 0.075 episodes per 100 patient-years with short-acting sulfonylureas. In addition, the odds ratio for severe hypoglycemia was 3.01 (95% confidence interval 1.35–6.77) for the long-acting versus the short-acting sulfonylureas.⁹ The Diabetes Outcome Progression Trial (ADOPT) showed that with glibenclamide (glyburide) the overall prevalence of hypoglycemia was 38.7% and that of severe hypoglycemic episodes 0.6%.¹⁰

One prospective study examined the prevalence of hypoglycemia in individuals with Type 2 diabetes treated with sulfonylureas. The study showed that over a 12-month period the prevalence of symptomatic hypoglycemia was 7%. However, a higher proportion (about 20%) of asymptomatic hypoglycemic episodes was detected using the continuous glucose monitoring system (CGMS).¹¹

In another study the CGMS was used to detect hypoglycemic events in subjects with Type 2 diabetes treated with sulfonylureas; the frequency of asymptomatic hypoglycemia lasting for at least 15 minutes was 56% over a period of 6 days.¹² Although hypoglycemia unawareness is more common in Type 1 diabetes, it may be more frequent in Type 2 diabetes than is appreciated.

Glibenclamide (glyburide) is associated with a greater risk of severe hypoglycemia than gliclazide because active metabolites prolong its hypoglycemic effects for 24 hours.^{3,13} Glibenclamide (glyburide) may also attenuate the glucagon response to hypoglycemia in patients with Type 2 diabetes.¹⁴

Glimepiride is associated with a lower risk of hypoglycemia in comparison with glibenclamide (glyburide). One multicenter European trial showed that glimepiride and the modified release form of gliclazide were associated with similar glycemic control. However, the modified release form of gliclazide was associated with fewer cases (3.7%) of mild or moderate hypoglycemia than glimepiride (8.9%) while no case of severe hypoglycemia was observed in either group.¹⁵

The risk of hypoglycemia with meglitinides is low. One head-to-head comparison of repaglinide and nateglinide showed that, over 4 months, the frequency of mild hypoglycemic episodes was 7% in the repaglinide group in comparison with no hypoglycemic episode in the nateglinide group.¹⁶ The same study showed slightly better improvement in HbA_{1c} with repaglinide than nateglinide.

Summary box

- The prevalence of all hypoglycemic episodes in patients treated with sulfonylureas is 20–40%
- The prevalence of severe sulfonylurea-induced hypoglycemia is much lower (0.4–0.6%)
- The prevalence of hypoglycemia is lower with sulfonylureas than with insulin
- Glibenclamide (glyburide) is associated with a higher risk for hypoglycemia, followed by glimepiride and the modified release form of gliclazide

Counter-regulation in hypoglycemia in Type 2 diabetes

People with Type 2 diabetes have greater protection against hypoglycemia because the counter-regulatory responses commence at higher blood glucose levels than in non-diabetic individuals¹⁷ (Figure 5.2) and in subjects with Type 1 diabetes.^{13,18} Previous studies examined the counter-regulatory responses to hypoglycemia in subjects

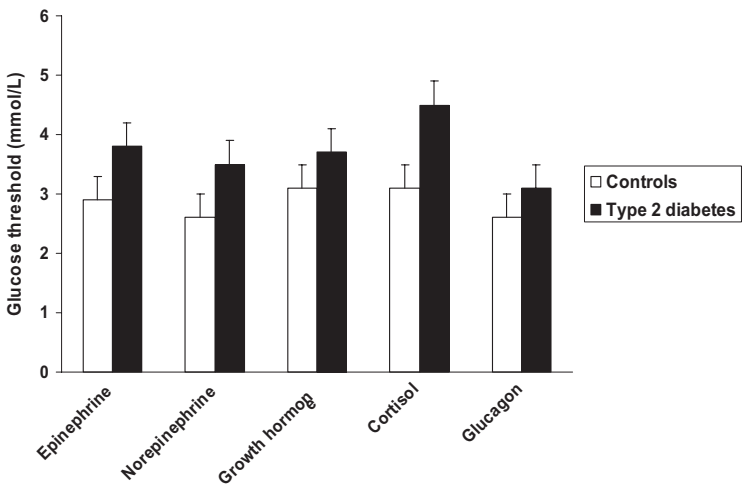


Figure 5.2 Mean (standard deviation) glucose thresholds for release of epinephrine, norepinephrine, growth hormone, cortisol, and glucagon in subjects without diabetes and in subjects with well-controlled Type 2 diabetes. All thresholds were statistically significantly higher in subjects with Type 2 diabetes than in controls.

with Type 2 diabetes who had been treated with diet alone or with sulfonylureas, and they were compared with subjects with Type 1 diabetes. These studies showed that the counter-regulatory hormones were released at higher glucose levels than in those with Type 1 diabetes.^{17–19}

The glucagon response to hypoglycemia is preserved in persons with Type 2 diabetes who are adequately controlled with oral anti-diabetic medications. However, patients with long-duration Type 2 diabetes who need insulin for treatment and in whom endogenous insulin secretion is low have diminished glucagon secretion in hypoglycaemia.¹⁹ That is, these patients behave like those with Type 1 diabetes, in whom glucagon secretion is impaired in the early stages of the disease.

Impaired hypoglycemia awareness has been associated primarily with Type 1 diabetes. However, antecedent hypoglycemia can also cause hypoglycemia unawareness in patients with Type 2 diabetes. An interesting study showed that antecedent hypoglycemia caused by a hypoglycemic insulin clamp diminished the magnitude of the symptomatic and neuroendocrine responses to any subsequent episode of hypoglycemia within the following 24–48 hours in subjects with Type 2 diabetes.²⁰

Aging is associated with blunted counter-regulatory responses to hypoglycemia and is itself an important risk factor for hypoglycemia. Thus, although counter-regulation usually begins at higher glucose thresholds in middle-aged patients with Type 2 diabetes, this is not the case for older patients. Although the symptomatic and counter-regulatory hormonal responses (growth hormone, cortisol, glucagon, and epinephrine) to hypoglycemia are modified by advancing age, it is not known at which age these changes become apparent.²¹

Summary box

- Counter-regulatory responses commence at higher blood glucose levels in people with Type 2 diabetes than in those with Type 1 diabetes
- The glucagon response to hypoglycemia is preserved in people with Type 2 diabetes treated with oral medications but is lost in long-lasting Type 2 diabetes
- In elderly people the counter-regulatory responses to hypoglycemia are impaired

Symptoms and signs of hypoglycemia in Type 2 diabetes

The symptoms of hypoglycemia are discussed in detail in Chapter 4. They do not differ between people with Type 1 and Type 2 diabetes. In addition, the agent inducing hypoglycemia (sulfonylurea or insulin) induces identical symptoms in patients with Type 2 diabetes whenever blood glucose is lowered in the same individual to the same level.^{22,23} However, in elderly people who have diabetes, symptoms of hypoglycemia may differ from those observed in younger individuals.²⁴ Generalized malaise, hypothermia, and a group of neurological symptoms including unsteadiness, sleepiness, poor coordination, blurred and/or double vision, slurred speech, and other focal neurological deficits have been identified in patients with Type 2 diabetes.^{13,24} These neurological symptoms and signs may be confused with other conditions such as stroke or vaso-vagal syncope. In addition, elderly people usually report lower symptom scores of hypoglycemia and limited perception of symptoms than younger individuals, with autonomic and neuroglycopenic symptoms being affecting equally.³ Two studies suggested that the attenuation in symptom intensity is a feature of increasing age, independent of any effects of diabetes.^{25,26}

Previous data confirmed that the glycemic threshold at which symptomatic responses to hypoglycemia are generated is altered with age.^{27,28} Thus, in younger people with Type 2 diabetes, symptoms are evoked at a blood glucose level of 65 mg/dl (3.6 mmol/L), which is on average 18 mg/dl (1.0 mmol/L) higher than the level at which cognitive function becomes impaired. This allows for action for correction of low blood glucose levels and prevention of neuroglycopenia. In older people, however, the glycemic threshold of

Summary box

- In elderly people with Type 2 diabetes hypoglycemia may manifest with neurological symptoms and signs including unsteadiness, poor coordination, blurred and/or double vision, slurred speech, and other focal neurological deficits
- The intensity of classic hypoglycemic symptoms may be lower in elderly people with Type 2 diabetes
- Elderly people may not have enough time to take action to correct hypoglycemia because symptoms occur late after the onset of neuroglycopenia

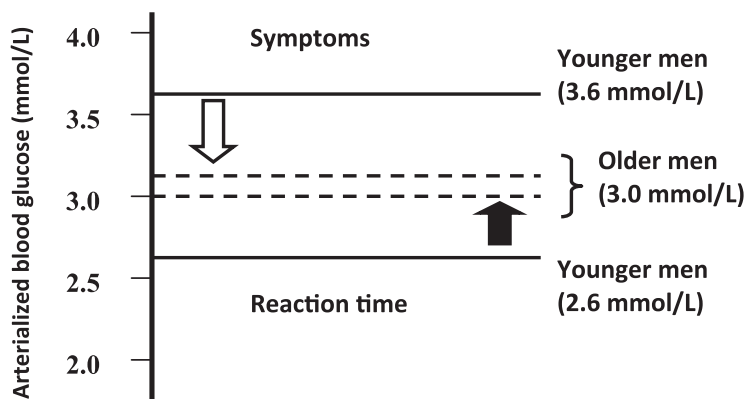


Figure 5.3 Glycemic thresholds for subjective symptomatic awareness of hypoglycemia and for the onset of cognitive dysfunction in younger and elderly males without diabetes. From reference 13.

symptomatic responses and that of the reaction time is close to 54 mg/dl (around 3.0 mmol/L), eliminating the time available for correction and prevention of severe hypoglycemia²⁷ (Figure 5.3).

Thus, in older people with diabetes, differences in symptoms, lower symptom intensity, and altered glycemic thresholds can predispose to severe hypoglycemia.

Treatment

In general, it is a good rule to regard all insulin secretagogues as having the potential to cause hypoglycemia and to inform patients and their families accordingly. The best way to prevent hypoglycemia is by frequent self-monitoring of blood glucose after initiation of a new therapy with insulin secretagogues and during periods of illness and reduced food intake. In case of doubt at home, it is always better for the patient to be treated for hypoglycemia than to ignore the possibility.

In elderly people and in those living alone, alternative treatment modalities should be considered such as dipeptidyl-peptidase inhibitors, glucagon-like 1 agonists, or insulin secretagogues with a low risk of hypoglycemia, instead of long-lasting sulfonylureas.²⁹ Particular attention should be paid to the concomitant medications the patients receive. Health care professionals should keep in mind that patients treated with sulfonylureas may not present with the

classic symptoms of hypoglycemia and that concomitant treatments may mask symptoms.

Mild hypoglycemic episodes due to sulfonylureas may be treated with simple carbohydrates, as described in Chapter 4, and a meal if it is close to that time, but the patient/carers should be aware of the possibility of repeated hypoglycemia over the next hours. Frequent self-monitoring of blood glucose is the key to treatment (Figure 5.4).

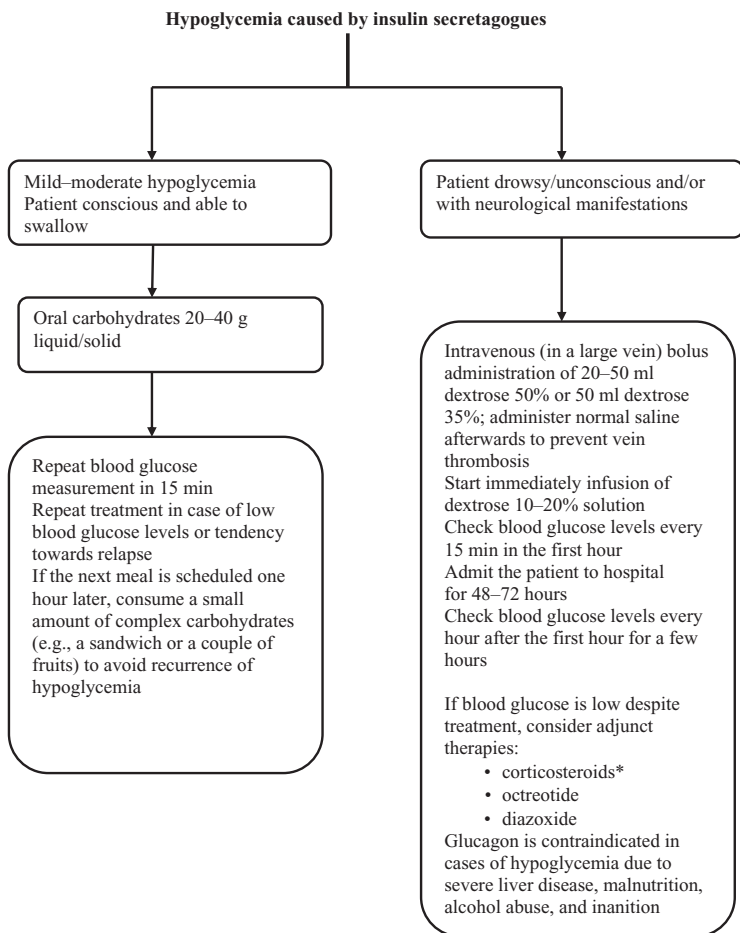


Figure 5.4 Proposed algorithm for the management of hypoglycemia caused by insulin secretagogues. *High doses of dexamethasone (with or without mannitol) are indicated in cases of cerebral edema as a complication of severe (usually from insulin) hypoglycemia.

Hypoglycemic coma caused by insulin secretagogues is not uncommon. Virtually every unconscious diabetic patient should be considered to be hypoglycemic until immediate estimation of the blood glucose levels has ruled it out.^{5,22}

When hypoglycemia occurs due to the use of sulfonylureas it can be potentially prolonged and require hospitalization. Intravenous bolus administration of 20–50 ml of 50% glucose solution or 50 ml of 35% glucose solution followed by infusion of 10–20% glucose solution should begin immediately and continued uninterrupted for one or more days. Blood glucose levels should be monitored frequently (see Figures 4.2a and 5.4). In the case of refractory hypoglycemia, addition of glucagon, hydrocortisone sodium, or diazoxide may be needed until the effects of the sulfonylurea have worn off. The duration of hospitalization depends on the sulfonylurea used and its duration of action. Thus, hospitalization and frequent glucose monitoring for 24–72 hours may be needed.²²

Data from the ACCORD trial showed that patients with Type 2 diabetes who experience symptomatic, severe hypoglycaemia are at increased risk of death, regardless of the intensity of glucose control.³⁰ Thus, hypoglycemia may be an important cause or contributing factor for death in 3–6% of patients with diabetes. The cause of death during hypoglycemia may be related to development of arrhythmia (frequent supraventricular and ventricular ectopic beats, prolongation of the QT interval and development of ventricular tachycardia, atrial fibrillation), silent myocardial ischemia, myocardial infarction, cerebral damage from glucopenia, and cerebral ischemia from acute thrombotic occlusion of the cerebral arteries.²¹ In one series, among 102 patients hospitalized for hypoglycemic coma, 92 patients had Type 2 diabetes and 50 of these patients had been treated with glibenclamide (glyburide) alone, 15 with the combination of glibenclamide (glyburide) and insulin, and 10 with glibenclamide (glyburide) and metformin.³¹ Sixty-two patients responded to treatment with intravenous glucose infusion during the first 12 hours, while 40 patients had protracted hypoglycemia of 12–72 hours' duration. Of note, severe head trauma and bone fractures were found in 8 patients, while transient asymptomatic myocardial ischemia was noticed in 2 patients; death occurred in 5 patients.³⁰ Because of increasing physical frailty and osteoporosis, elderly patients are more susceptible to physical injury during hypoglycaemia, and bone fractures, joint dislocations, soft tissue injuries, and head injuries are not uncommon.²¹

Summary box

- Regard all insulin secretagogues as having the potential for hypoglycemia and inform patients and their families accordingly
- Medications with a low risk of hypoglycemia should be preferred in older people with Type 2 diabetes
- Manage every unconscious diabetic patient as hypoglycemic until immediate estimation of blood glucose levels rules it out
- Hypoglycemia due to sulfonylurea may be prolonged and needs continuous intravenous glucose infusion and hospitalization for 24–72 hours

Case studies**Case study 5.1**

A 76-year-old female patient was admitted to the orthopedic unit for right hip replacement. She had been treated with glibenclamide (glyburide) 5 mg twice daily and metformin 1 g/day. In the morning of the admission day and after she had taken her diabetes medications at home, she complained of nausea, vomiting, and diarrhea and refused any food intake. In the afternoon the patient was found in bed in coma. Computed tomography of the brain was normal. Blood was sent to the laboratory for biochemical analysis; after about 2 hours the laboratory informed the unit that the patient's blood glucose was 20 mg/dl (1.1 mmol/L).

What was wrong with this patient?

Glibenclamide (glyburide) is a well-known sulfonylurea that may cause severe hypoglycemia more often than other sulfonylureas due to the prolonged duration of action of the medication and its metabolites. The relatives should have been informed about the risk of hypoglycemia with glibenclamide (glyburide) and they should have informed the personnel of the unit that the patient had taken her medications before admission.

Blood glucose should have been closely monitored in the hospital and, if it was low, intravenous glucose infusion should have begun. In addition, every unconscious patient should be considered as hypoglycemic, especially if the patient has diabetes, until immediate estimation of the blood glucose levels rules out hypoglycemia. Thus the patient should have been managed as having been in hypoglycemic coma until the results of the blood test were available.

How will you manage this patient?

The patient was unconscious, thus a bolus of 20–50 ml of 50% glucose solution or 50 ml of 35% glucose solution, followed by infusion of 10–20% glucose solution should begin with frequent monitoring of blood glucose.

What was the outcome?

Despite the increase in blood glucose levels after intravenous infusion of glucose solution 10%, the patient's brain function never recovered. Severe and prolonged hypoglycemia may cause neuronal death, resulting in permanent impairment of brain function. If hypoglycemia is treated early and effectively, apparent full recovery is the rule, even after severe episodes of hypoglycemia.

Case study 5.2

An 82-year-old male patient was taken to the emergency room in the afternoon for loss of consciousness in the previous hour. The patient had hypertension, chronic ischemic heart disease, and mild diabetes treated with 30 mg gliclazide MR daily. On examination the patient had coma (Glasgow scale 5) and right hemiplegia.

How will you manage this patient?

An immediate blood glucose determination in the emergency room using a portable glucose meter was 30 mg/dl (1.7 mmol/L). A bolus injection of 50 ml 35% glucose solution was given followed by infusion of 10% glucose solution. The patient recovered fully and no neurological deficits were detected 30 minutes after correction of hypoglycemia. The results of the blood tests from the laboratory 1 hour later confirmed hypoglycemia.

What was the cause of hypoglycemia?

The patient was living alone and his relatives took care of him once daily, usually in the afternoon. Although the risk of hypoglycemia with gliclazide is lower than with other long-acting sulfonylureas, it may still occur under certain circumstances. The patient did not remember if he had eaten his breakfast and lunch. The relatives noticed that the patient had eaten a small amount of his breakfast and no lunch. Thus, the cause of hypoglycemia was reduced food intake together with treatment with gliclazide.

When will you discharge this patient?

Every patient with hypoglycemia caused by insulin secretagogues should be hospitalized for 24–72 hours, managed with intravenous

glucose infusion, and have frequent blood glucose monitoring. In case of early discharge, hypoglycemia may recur, especially in patients taking long-lasting sulfonylureas.

Case study 5.3

A 71-year-old male patient with Type 2 diabetes complained of frequent episodes of symptomatic hypoglycemia in the previous week manifesting as excess sweating, feeling of hunger, and tremor. His diabetes control was excellent (HbA_{1c} 6.5%) with glimepiride 4mg daily and metformin 2g daily. His renal function was normal and he did not have microalbuminuria. No changes in dietary habits and exercise program were reported. The patient noticed that the hypoglycemic episodes commenced after initiation of propranolol for supraventricular tachycardia.

What is the cause of hypoglycemia?

Non-selective β -adrenergic blockers such as propranolol have been associated with hypoglycemia in patients treated with insulin or sulfonylureas. Data from the literature suggest that it is difficult to prove a cause and effect relationship between therapy with β -adrenergic blockers and hypoglycemia. However, β -adrenergic blockers can increase glucose uptake in skeletal muscle by antagonizing the effects of catecholamines on glucose uptake and lipolysis. In addition, suppression of lipolysis and reduction in non-esterified fatty acids in plasma improve insulin sensitivity and indirectly reduce gluconeogenesis. On the other hand, β -adrenergic blockers decrease insulin secretion. Thus, the effect of these medications on diabetes may be towards low or high blood glucose levels. β -adrenergic blockers were not associated with higher risk for hypoglycemia in the UKPDS.³² In addition, β -adrenergic blockers can block the adrenergic response to hypoglycemia and delay recovery because of inhibition of catecholamine-mediated glucose counter-regulation.

In this patient no other apparent cause of hypoglycemia could be found and it was attributed to propranolol.

How will you manage this patient?

Propranolol was discontinued and a selective β -adrenergic blocker was initiated. Hypoglycemic episodes stopped and no recurrences were observed.

Drug interactions from concomitant treatments can cause severe episodes of hypoglycemia in people with Type 2 diabetes treated with insulin secretagogues. Physicians should be aware

of these drug interactions and they should inform patients of the need for frequent self-monitoring when additional treatments are necessary.

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CHAPTER 6

Lactic acidosis in diabetes

Nikolaos Tentolouris, Nikolaos Katsilambros

Introduction

Lactate is normally produced by most of the body cells by the reduction of pyruvate in small quantities as a result of anaerobic glucose metabolism.¹ Under basal conditions, lactate production is ~1300 mmol/day for a 70-kg person.¹ The normal lactate to pyruvate ratio is 20:1. Under hypoxic conditions, pyruvate is preferentially reduced to lactate, and the lactate/pyruvate ratio increases. The normal arterial blood lactate levels are approximately 0.620 mmol/L and the venous lactate levels are slightly higher, at 0.997 mmol/L.² Blood lactate is normally cleared by the liver, kidney, and skeletal muscles. The liver is the primary site of lactate clearance and can metabolize up to 100 mmol/h, or 60% of the circulating lactate, under normal conditions. In the liver, lactate is converted to glucose to serve as an energy source during periods of hypoxia³ (Figure 6.1). Approximately 20–30% of the daily lactate load is metabolized by the kidneys.⁴ Renal clearance is increased in acidosis and is maintained even in the presence of low renal perfusion. Renal lactate clearance is primarily through metabolism and not excretion.⁵ Small increases in blood lactate levels are called hyperlactemia (blood lactate levels >2.5 mmol/L). When lactate is produced in large quantities (blood lactate concentrations >5 mmol/L) due to various pathological conditions, lactic acidosis develops, which is considered a distinct form of metabolic acidosis.^{1,2}

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Summary box

- Small quantities of lactate are produced normally during the anaerobic metabolism of glucose
- The normal blood lactate concentrations are $<2\text{ mmol/L}$
- Small increases in blood lactate levels ($>2.5\text{ mmol/L}$) are called hyperlactemia
- In lactic acidosis, blood lactate levels are $>5.0\text{ mmol/L}$
- The liver and kidneys are the main organs that metabolize lactate

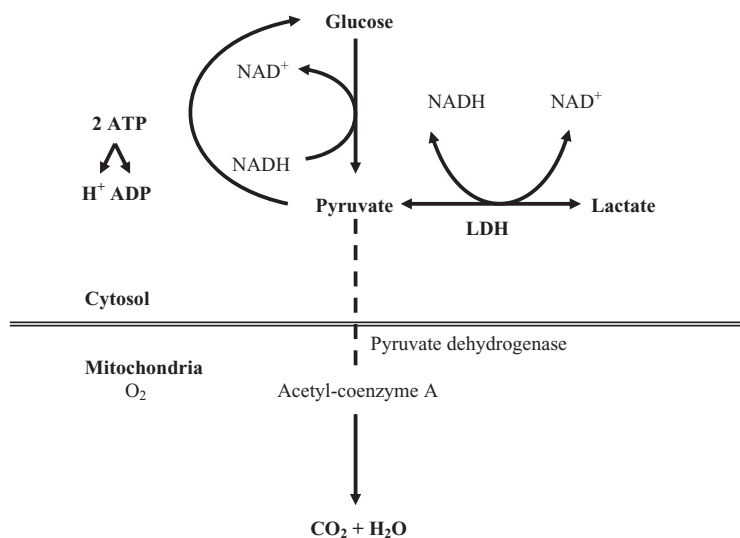


Figure 6.1 Biochemistry of lactate production and metabolism. Glycolysis through anaerobic metabolism results in the production of pyruvate. Pyruvate can then follow one of the following pathways: 1) it can be converted back to glucose in the liver and kidney through the Cori cycle; 2) it can enter the mitochondria in the presence of oxygen and be metabolized to CO_2 and water through the Krebs cycle; 3) it can be reduced to lactate. Lactate can be converted back to pyruvate by lactate dehydrogenase (LDH), which can then follow one of the pathways described above. Under anaerobic conditions and situations in which the ratio of reduced nicotinamide adenine dinucleotide (NADH) to oxidized nicotinamide adenine dinucleotide (NAD^+) is increased, pyruvate is reduced to lactate. ADP, adenosine diphosphate.

Pathogenesis

Most cells in the body normally “burn” glucose to form water and carbon dioxide. This is a two-step process. First, glucose is broken down to pyruvate through glycolysis. Then, mitochondria oxidize the pyruvate into water and carbon dioxide by means of the Krebs cycle and oxidative phosphorylation. This second step requires oxygen. The net result is ATP, the energy carrier used by the cell.¹

When the energy in ATP is utilized (ATP hydrolysis to adenosine diphosphate and inorganic phosphate [Pi]), a hydrogen ion is released. For every mole of glucose metabolized anaerobically, 2 moles of hydrogen ion are produced.² Both ADP and Pi are re-used as anaerobic glycolysis continues. The mitochondria normally incorporate these hydrogen ions back into ATP, thus preventing build-up of hydrogen ions and maintaining neutral pH. If oxygen supply is inadequate, the mitochondria are unable to continue ATP synthesis at a rate sufficient to supply the cell with the required ATP. In this situation, glycolysis is increased to provide additional ATP, and the excess pyruvate produced is converted into lactate and released from the cell into the blood stream, where it accumulates over time.¹ When excess lactate, which is the anionic form of lactic acid, is released into the blood, maintenance of electroneutrality requires a cation (hydrogen) to be released as well. This can reduce blood pH. While increased glycolysis helps compensate for less ATP from oxidative phosphorylation, it cannot bind the hydrogen ions resulting from ATP hydrolysis. Therefore, the hydrogen ion concentration rises and causes acidosis. Hypoxia causes both excess lactate production and acidification, and lactate is therefore a good “marker” of hypoxia, but lactate itself is not the cause of low pH.^{1,2}

Lactic acidosis develops when the production of lactate exceeds its utilization. In addition, there is evidence that in significant lactic acidosis the uptake and metabolism of lactate by the liver is decreased and the liver becomes a lactate-producing organ.¹

Homeostatic mechanisms towards elimination of excess lactate production during acidosis include the inhibition by intracellular acidosis of 6-phospho-fructokinase, one of the key enzymes in glucose metabolism, limiting the production of lactate. An additional mechanism is the increased gluconeogenesis in the renal cortex by increased activity of the rate-limiting enzyme phosphoenolpyruvate carboxykinase.⁶ Even in the setting of marked

hypoperfusion, lactate can be effectively removed by the kidney through this pathway.^{7,8} Figure 6.1 depicts the biochemistry of lactate production and metabolism.

Summary box

- Lactate per se does not cause acidosis
- Acidosis during the anaerobic metabolism of glucose is the result of ATP hydrolysis and excess release of lactate and hydrogen ions into the blood stream
- Lactic acidosis develops when production of lactate exceeds its utilization

Clinical presentation

The onset of lactic acidosis may be either abrupt or insidious. Initial symptoms often include nausea, vomiting, and abdominal pain. In more insidious cases fatigue and weight loss may predominate. Subsequently, deep and rapid breathing, hypotension, tachycardia, altered mental status, liver and/or renal failure, clotting abnormalities, seizures, and cardiac arrhythmia ensue. Usually, the symptoms of the underlying, often severe, disease coexist.^{1,2}

Summary box

- The clinical presentation of lactic acidosis is that of metabolic acidosis
- Usually, symptoms and signs of the underlying disease coexist

Classification

Lactic acidosis is classified into two categories: Type A and Type B.⁹ Type A is associated with hypoperfusion and hypoxia and is more common. Shock from various causes (rapid blood loss, cardiogenic shock, sepsis), severe anemia, carbon monoxide poisoning, and grand mal seizures may cause Type A lactic acidosis.³ The causes of Type A lactic acidosis are shown in Box 6.1.

Type B lactic acidosis is not associated with systemic hypoperfusion. Many diseases (genetic diseases, Type 2 diabetes mellitus, liver disease, renal failure, malignancy, sepsis, thiamine deficiency,

Box 6.1 Causes of Type A lactic acidosis**Decreased oxygen delivery**

- Hypotension
- Volume depletion
- Blood loss
- Cardiogenic shock
- Septic shock
- Severe anemia
- Severe hypoxemia
- Carbon monoxide poisoning

Increased oxygen demands

- Exercise
- Seizures
- Shivering

severe hypoglycemia, and pheochromocytoma), drugs, and toxins are associated with it.⁹ The incidence of any type of lactic acidosis in patients with diabetic ketoacidosis is quite low.¹⁰ The causes of Type B lactic acidosis are shown in Boxes 6.2 and 6.3.

Regarding Type 2 diabetes mellitus, it is unclear whether diabetes per se predisposes patients to lactic acidosis. However, there is evidence that oxidation of lactate is reduced by 75% in skeletal muscle in experimental animals¹¹ and that in patients with Type 2 diabetes basal lactate levels are higher than in subjects without diabetes.¹²

The occurrence of Type B lactic acidosis with biguanide therapy is low and is about 10 times lower with metformin than phenformin.^{13,14} Metformin directly inhibits complex I of the mitochondrial respiratory chain and gluconeogenesis.¹ Extensive worldwide experience indicates that the incidence of lactic acidosis with metformin is 0.03 cases per 1000 patient-years of treatment, with a mortality rate of 50%.¹⁴⁻¹⁷ It is not usually due to the drug but to predisposing conditions such as severe liver, renal, or cardiac disease.¹⁰ Metformin should not be given to patients with advanced renal or liver disease or to those with cardiac decompensation. As a general rule, metformin should not be given to patients with serum creatinine >1.4 mg/dl (123 μ mol/L) for women or >1.5 mg/dl (132 μ mol/L) for men.¹⁸ However, because renal function assessed by determination of glomerular filtration rate (GFR) is related only

Box 6.2 Causes of Type B lactic acidosis**Inadequate oxygen utilization**

- Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome
- Fructose 1,6-diphosphatase deficiency
- Pyruvate dehydrogenase deficiency
- Mitochondrial myopathies
- Systemic inflammatory response syndrome
- Type 2 diabetes mellitus
- Severe liver disease
- End-stage renal disease
- Severe hypoglycemia
- Diabetic ketoacidosis
- Malignancy
- Total parenteral nutrition
- Thiamine deficiency
- HIV infection
- Malaria
- Drugs/toxins (see Box 6.3)

Other

- D-lactic acidosis

Box 6.3 Drugs and toxins associated with lactic acidosis

- | | |
|-----------------------|---|
| • Biguanides | • Nucleoside reverse transcriptase inhibitors |
| • Ethanol | • Propylene glycol |
| • Propofol | • Vasoactive drugs |
| • β_2 -agonists | • Theophylline |
| • Salicylate | • Isoniazid |
| • Niacin | • Nalidixic acid |
| • Simvastatin | • Acetaminophen |
| • Cyanide | • Nitroprusside |
| • Lactulose | • Linezolid |

loosely to serum creatinine and because the relationship is influenced by age, weight, and creatinine production, it is recommended that in patients >80 years of age, GFR should be determined in a 24-h urine collection before prescribing metformin. In all other cases GFR should be calculated using the modification of diet in renal disease (MDRD) formula.¹⁸ For normal renal function or for stage 1 and 2 chronic kidney disease (GFR >60 ml/min per 1.73 m²), full doses of metformin are reasonable. For patients with stage 3 chronic kidney disease (GFR 30–59 ml/min per 1.73 m²), half-maximal doses of metformin are arguably reasonable. For patients with stage 4 and 5 chronic kidney disease (GFR <30 ml/min per 1.73 m²), metformin should be avoided. Renal function should be checked at least yearly during metformin therapy.¹⁸

Concerning heart failure, in 2006, the U.S. Food and Drug Administration listed heart failure as a precaution rather than a contraindication for the prescription of metformin.¹⁹ In 2010, the guidelines from the American Diabetes Association stated that metformin may be used in patients with stable congestive heart failure if renal function is normal and that it should be avoided in unstable hospitalized patients with congestive heart failure.²⁰ Actually, there is a paucity of data from prospective studies to answer the question whether metformin is safe in patients with heart failure. Therefore, it is difficult to ascertain the effects of metformin on the incidence of lactic acidosis and clinicians are advised to weigh the potential risks and benefits of using metformin in patients with heart failure.

To minimize the risk of lactic acidosis in hospitalized patients, metformin should be withheld from those at risk.¹⁰ It should be temporarily discontinued for about 48 h during/after the use of an intravascular contrast medium, until normal function is re-established.^{10,18} In addition, metformin should be withheld during major surgery (risk of hypoperfusion with anaerobic metabolism and lactate production), critical limb ischemia (anaerobic metabolism and lactate generation), liver disease (impaired lactate metabolism), cardiorespiratory failure with hypoxia, general anesthesia in patients with autonomic failure (high risk of hypotension), history of lactic acidosis, and alcohol abuse.¹⁰

D-lactic acidosis is a unique form of lactic acidosis. It occurs in patients with short bowel syndrome or a history of jejunio-ileal bypass surgery for morbid obesity.²¹ The syndrome is characterized by episodes of neurological symptoms, a high anion gap metabolic acidosis, and normal lactate levels. Because the assay for lactate

measurement uses a stereoscopic L-lactate dehydrogenase enzyme, only L-lactate is measured. The normal levels of L-lactate in the blood and urine are 0–0.25 mmol/L. D-lactic acidosis is due to overproduction of D-lactate by *Lactobacillus acidophilus* and can be exaggerated after consumption of a high-carbohydrate meal or treatment with broad-spectrum antibiotics without activity against this pathogen such as trimethoprim–sulfamethoxazole, doxycycline, or kanamycin. D-lactate has the potential to accumulate because humans lack D-lactate dehydrogenase and rely on clearance of D-lactate by renal excretion. If there is clinical suspicion for D-lactic acidosis, D-lactate levels must be specifically requested.²⁰

Recent data suggest that linezolid, an antimicrobial used for the management of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecalis*, and as second-line therapy for mycobacterial infections, can cause lactic acidosis within the first 3 weeks or later of its use.²² As linezolid may be used for the management of diabetic foot infections caused by MRSA, attention should be paid to such patients presenting with metabolic acidosis and the possibility of lactic acidosis should be considered.

Summary box

- Lactic acidosis is classified as Type A and Type B
- Type A is much more common and is associated mainly with decreased oxygen delivery
- Type B is due to many diseases, drugs, and toxins
- Lactic acidosis due to metformin is rare in diabetes
- To minimize the risk of lactic acidosis in diabetes, metformin must be prescribed after evaluation of renal function and discontinued in patients at risk for renal, liver, or cardiorespiratory failure

Diagnosis

The diagnosis of lactic acidosis is based on the following criteria:^{1,2}

- blood lactate levels >5 mmol/L
- arterial pH <7.35.

Lactic acidosis is associated with an elevation in the anion gap. If the anion gap is >35 mEq/L, then lactic acidosis should be a strong consideration in the absence of intoxication with ethylene glycol or methanol.¹⁰ However, because the anion gap is mainly determined by the negatively charged proteins, especially albumin, low serum albumin levels, a common finding in critically ill patients, can lower

the anion gap and mask a high anion gap metabolic acidosis. The calculated anion gap should therefore be increased by 2.5 mEq/L for every 1.0 g/dl (10 g/L) decrease in serum albumin levels less than 4.0 g/dl (40 g/L).²³

Likewise, because lactic acidosis can frequently be associated with a concomitant respiratory or metabolic alkalosis, the arterial pH can be higher and an insensitive indicator of lactic acidosis. Therefore, the pH may be low, normal, or even elevated in lactic acidosis.¹

Other biochemical abnormalities include low bicarbonate levels (usually the base deficit is >6 mmol/L), elevated lactate dehydrogenase concentration, and often (but not invariably) elevated hepatic transaminase and creatinine kinase levels.²³

Summary box

The diagnosis of lactic acidosis is based on the following criteria:

- blood lactate levels >5 mmol/L
- arterial pH <7.35

Treatment

Lactic acidosis carries a 50% mortality rate.^{2,4,5} There are no evidence-based guidelines for the treatment of lactic acidosis despite progress in our understanding of its pathophysiology. Metformin should be immediately discontinued in every patient with lactic acidosis. In general, as these patients have all the hallmarks of severe vascular collapse, effective management of the predisposing disease together with efforts to maintain cardiac output, blood pressure, oxygenation, and renal perfusion should be undertaken.¹⁰ Efforts for the correction of the arterial pH are warranted because acidosis results in reduction in cardiac output, reduced response to catecholamines, abnormal hepatic metabolism, and arrhythmias. However, there is an argument against the routine use of bicarbonate in patients with lactic acidosis because of the potential to worsen hypokalemia, hypocalcemia, and intracellular acidosis, possibly resulting in sodium overload, rebound alkalosis, and further lactate production.^{5,7} Carbicarb is a buffer solution containing an equimolar mixture of sodium bicarbonate (NaHCO_3) and sodium carbonate (Na_2CO_3). It has the advantage over bicarbonate that it does not generate CO_2 and therefore does not worsen intracellular acidosis. It is thus an attractive option for the correction of acidosis in lactic acidosis. However, there is limited clinical

experience in humans with lactic acidosis and carbicarb is not available in many countries.²⁴ Dichloroacetate (DCA) can increase the oxidative metabolism of pyruvate in mitochondria by stimulating the pyruvate dehydrogenase complex. A randomized, placebo-controlled trial of DCA in the treatment of lactic acidosis showed improvement in blood lactate concentration and pH in the group receiving DCA with no difference in mortality rates. The use of the drug may be more beneficial in the early stages of lactic acidosis, when lactate levels are <5 mmol/L.²⁵

The use of hemodialysis does not seem to alter mortality in patients with lactic acidosis due to metformin. However, this may be due to the fact that this type of treatment is offered to more critically ill patients or to those who have co-morbidities or more severe acidosis. Therefore, hemodialysis may be of benefit in patients with metformin-associated lactic acidosis. An advantage of hemodialysis is that it partially removes metformin from the circulation which is of clinical relevance in patients with high metformin blood levels.^{4,5,7,26,27}

Summary box

- Lactic acidosis carries a high mortality rate
- Treatment of the underlying disease is the mainstay of therapy together with efforts to maintain cardiac output, blood pressure, oxygenation, and renal perfusion
- The routine use of bicarbonate is not recommended
- The use of dichloroacetate and hemodialysis may be beneficial

Case studies

Case study 6.1

A 77-year-old man with Type 2 diabetes mellitus diagnosed 5 years earlier was admitted to the emergency room after 3 days of worsening abdominal pain and vomiting. On the day of admission he reported weakness, dizziness, and blurred vision. His wife noticed also slurred speech and confusion. The patient had nausea and diarrhea 7 days before his admission, for 3 days, attributed to viral gastroenteritis. He was using metformin 2.5 g/day for his diabetes. He also had arterial hypertension, dyslipidemia, background diabetic retinopathy, and nephropathy, with a 24-h protein

excretion rate of 0.35 g; serum creatinine in the past was 1.3 mg/dl (114.9 μ mol/L).

On examination his blood pressure was 105/70 mmHg, pulse rate 105 beats per min (reference 60–100 beats per min), respiratory rate 29 breaths per min (reference 14–20 breaths per min), and core temperature 36.7°C (98.1°F). His chest X-ray and electrocardiogram (ECG) were normal. Initial laboratory investigations showed a creatinine of 4.6 mg/dl (406.64 μ mol/L) (reference 0.6–1.2 mg/dl; 53–106 μ mol/L), urea 160 mg/dl (27.2 mmol/L) (reference 10–50 mg/dl; 1.7–8.3 mmol/L), sodium 138 mEq/L, potassium 3.8 mEq/L, glucose 124 mg/dl (6.9 mmol/L), and chloride 103 mEq/L. Complete blood count was within the normal range. Arterial gas showed pH 6.87, PaO₂ 105 mmHg, PCO₂ 14 mmHg, SaO₂ 98%, and HCO₃⁻ 8.4 mEq/L.

What is your diagnosis?

The patient has severe renal impairment and metabolic acidosis. The deterioration of his renal function was probably due to dehydration from gastroenteritis. In order to make a differential diagnosis of metabolic acidosis, one has to calculate the anion gap. It is usually calculated from the following formula:

$$([\text{Na}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-]).$$

The normal value of the gap is 12(\pm 3) mEq/L. An increase in anion gap is most commonly caused by addition of an acid salt which reduces plasma bicarbonate concentration.

Using the above formula, the anion gap is calculated as 26.6 mEq/L, which is an anion gap metabolic acidosis.

What are the causes of anion gap metabolic acidosis?

The causes of anion gap metabolic acidosis are:

- Ketoacidosis
- Uremia
- Paraldehyde
- Diabetes
- Lactic acidosis
- Ethylene glycol
- Alcoholism
- Toxins
- Methanol

- Starvation
- Salicylates

What is the cause of metabolic acidosis in this patient?

In a patient with an anion gap metabolic acidosis and renal impairment who is treated with metformin, lactic acidosis should be included in the differential diagnosis. The arterial lactate levels in this patient were 16 mmol/L. Thus, a diagnosis of lactate acidosis was made.

How could lactic acidosis be prevented in this patient?

Prescription of metformin requires calculation of the GFR. This can be calculated using the MDRD formula as follows:

For creatinine in mg/dl:

$$\text{GFR (ml/min per } 1.73 \text{ m}^2) = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \\ \times [0.742 \text{ if female}] \times 1.210 [\text{if black}]$$

For creatinine in $\mu\text{mol/L}$:

$$\text{GFR (ml/min/} 1.73 \text{ m}^2) = 32788 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \\ \times [0.742 \text{ if female}] \times 1.210 [\text{if black}]$$

Creatinine levels in $\mu\text{mol/L}$ can be converted to mg/dl by dividing them by 88.4. The 32788 number above is equal to $186 \times 88.4^{1.154}$.

Using this formula, the GFR of the patient before his illness was 57 ml/min per 1.73 m^2 . The patient had stage 3 chronic kidney disease (GFR 30–59 ml/min per 1.73 m^2) and, therefore, half-maximal doses of metformin would be reasonable. However, on admission his GFR was only 13 ml/min per 1.73 m^2 and metformin is contraindicated. In addition, metformin should be withheld after the onset of gastroenteritis, which caused rapid deterioration of renal function due to dehydration.

How will you manage this patient?

The patient was admitted to the renal unit with the diagnosis of pre-renal acute renal failure and metformin-associated lactic acidosis. Metformin was discontinued immediately and insulin treatment was initiated. He was treated with hydration and renal replacement therapy every second day using a high-flux dializer membrane and administration of sodium bicarbonate via hemofiltration. Four hours after hemodialysis his acidosis improved (pH 7.43) and lactate levels had halved. Seven days later they were 1.20 mmol/L. The

patient was discharged from hospital with a serum creatinine 1.4 mg/dl (123.8 μ mol/L).

Case study 6.2

A 68-year-old woman with long-standing Type 2 diabetes mellitus was admitted to the coronary care unit for acute myocardial infarction. The patient was treated with basal insulin once daily, pre-meal rapid-acting insulin, and metformin 2.5 g/day. She had also hypertension, dyslipidemia, and coronary artery disease.

On admission, her blood pressure was 105/50 mmHg, pulse rate 68 beats per min (reference 60–100 beats per min), respiratory rate 20 breaths per min (reference 14–20 breaths per min), and core temperature 36.4°C (97.5°F). On admission her blood glucose was 420 mg/dl (23.3 mmol/L), creatinine 1.2 mg/dl (106.08 μ mol/L), Na 140 mEq/L, potassium 4.2 mEq/L, and chloride 106 mEq/L. Treatment with insulin was initiated. Because the condition of the patient was stable and her blood glucose levels were high, metformin was not discontinued. On the same day the patient was submitted to coronary angiography for percutaneous transluminal angioplasty with stenting to the left anterior descending artery. Two days later she was oliguric and complained of nausea and abdominal pain, her breathing progressively became deep and rapid, and her mental status deteriorated. New biochemical tests showed creatinine 3.4 mg/dl (300.56 μ mol/L), sodium 138 mEq/L, potassium 4.2 mEq/L, and chloride 108 mEq/L. Arterial gas showed pH 7.01, PaO₂ 94 mmHg, PCO₂ 18 mmHg, SaO₂ 96%, and HCO₃⁻ 8 mEq/L. Arterial lactate levels were 15 mmol/L.

What is your diagnosis?

The patient developed acute renal failure (acute tubular necrosis) due to contrast medium injection for the coronary angiogram and lactic acidosis (acidosis with increased lactate levels) due to concomitant treatment with metformin. Because of the acute myocardial infarction and the risk of fluid overload, no adequate hydration was performed before angiogram to minimize the risk of acute tubular necrosis from the contrast medium.

Could lactic acidosis have been prevented?

In patients who are hemodynamically unstable and in whom there is a risk of acute cardiac decompensation, metformin should be discontinued until the patient is stable. Metformin can then safely

be re-administered. Metformin should have been discontinued before the angiogram and for 1 or 2 days afterwards to minimize the risk of lactic acidosis and only restarted after re-evaluation of renal function.

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CHAPTER 7

Management of hyperglycemia in the hospital

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Introduction

Patients with diabetes represent a high proportion of hospitalized individuals. This is not surprising, since diabetes increases the risk for disorders that often require hospitalization, including cardiovascular diseases, nephropathy, several types of infection, and lower extremity amputations. It has been repeatedly reported that diabetic patients are more likely to be hospitalized than persons without diabetes, although diabetes is often diagnosed at admission or during hospitalization for different reasons, even for hyperglycemia itself.^{1,2} It has recently been reported that 22% of all hospital inpatient days in the United States are incurred by people with diabetes and that hospital inpatient care accounts for nearly 50% of all medical expenditure for diabetes management.³ The prevalence of diabetes among hospitalized patients has been estimated at 12.5–24%,⁴ although the accuracy of these numbers has been questioned due to methodological problems associated with accurate diagnosis of the disease in a stressful situation.

The importance of in-hospital glycemic control

Hospitalized individuals make up a distinct, albeit heterogeneous, cohort, being comprised of patients with diverse diseases and dif-

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ferent needs. Illness and/or surgery often lead to hyperglycemia by triggering counter-regulatory hormones, i.e., hormones that counteract insulin action. Furthermore, fasting, inactivity, the use of certain drugs such as glucocorticoids, parenteral nutrition and IV glucose infusions also contribute to the development of hyperglycemia during hospitalization.

In-hospital hyperglycemia results from three distinct situations:

- Decompensation of pre-existing diabetes
- Newly diagnosed (previously unknown) diabetes
- Stress hyperglycemia (resolving after discharge from the hospital).

Hyperglycemia, if severe, induces osmotic diuresis, which in turn leads to dehydration and electrolyte disturbances. When increased blood glucose is accompanied by marked insulin deficiency (as in Type 1 or advanced Type 2 diabetes), accelerated lipolysis and ketogenesis may lead to the development of diabetic ketoacidosis (see Chapters 1 and 2). In older patients with Type 2 diabetes, severe dehydration may develop, leading to a hyperosmotic state (see Chapter 3). In addition, even moderately high blood glucose levels exert deleterious effects on the body via several mechanisms. It has been shown that hyperglycemia harms the immune system by affecting both phagocyte function and cellular immunity, leading to increased susceptibility to infection.⁵ In addition, high blood glucose has been associated with endothelial dysfunction and prothrombotic changes, both states increasing the risk for cardiovascular damage.^{6,7} Increased oxidative stress is also believed to be a key pathophysiological mechanism mediating tissue injury related to hyperglycemia.⁸

The catabolic state accompanying every acute illness or major surgery (due to decreased nutrition and high circulating levels of counter-regulatory hormones) deteriorates in the absence of insulin (either absolute or relative), a hormone with well-known anabolic effects.⁹

Several observational studies have shown that hyperglycemia in hospital settings is associated with increased mortality and several adverse outcomes, such as prolonged in-hospital stay, infections, delayed wound healing, and cardiovascular events.⁴ It should be kept in mind, however, that although proper adjustments have been performed during observational studies, the well-established association between hyperglycemia and poor outcome cannot be proven to be causal. Patients with poor outcome might present

elevated blood glucose levels due to the severity of their condition itself. In other words, disease severity is reflected in blood glucose, both in diabetic and non-diabetic patients.

Apart from control of in-hospital glycemia, an increasingly large body of evidence supports the beneficial effect of insulin therapy in acute settings. Whether these benefits are the result of a direct pharmacological effect attributed to insulin or just an indirect effect caused by improved glycemia, enhanced glycolysis, or suppressed lipolysis, remains controversial. Many experts agree, however, that in-hospital insulin therapy has significant potential for benefit.^{4,9–10} Even though it has become apparent that severe hyperglycemia should be aggressively treated in order to avoid catastrophic complications, the question of “how low should we go” arises when blood glucose falls below 200mg/dl (11.1 mmol/L) and hypoglycemia appears as a potential adverse effect of therapy.

Randomized clinical trials (RCT) have been presented as a solution to such arguments. Indeed, several trials have addressed the question of “how low” blood glucose values should be in order for hospitalized patients to receive treatment. These studies, however, have been performed almost exclusively in critically ill patients, being hospitalized in a medical, surgical or cardiovascular intensive care unit (ICU).¹¹ While results remain controversial, one study performed in a surgical ICU showed decreased mortality with intensive insulin therapy aimed at near-normal plasma glucose levels (80–110mg/dl [4.4–6.1 mmol/L]),¹² whereas subsequent studies failed to confirm that finding.¹¹ In the largest multi-center, multi-national RCT to date, including both surgical and medical ICU patients, mortality rates were significantly higher for the intensively treated (mean blood glucose achieved: 115 mg/dl [6.4 mmol/L]) than the conventionally treated group (mean blood glucose achieved: 145 mg/dl [8.1 mmol/L]).¹³

These data suggest that although hyperglycemia should be carefully managed in the hospital setting, aiming at very tight glycemic targets significantly increases the risk of severe hypoglycemia, which may actually harm. A detailed discussion on this topic is beyond the scope of the present book and the reader is referred to recent extensive reviews of the subject.^{4,13–15}

A recent consensus statement published by the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE)¹³ proposed that inpatient glycemic control should focus on the following targets:

- Critically ill patients: 140–180 mg/dl (7.8–10 mmol/L)
- Non-critically ill patients:
 - Premeal: <140 mg/dl (7.8 mmol/L)
 - Random: <180 mg/dl (10 mmol/L).

It should be emphasized, however, that glycemic targets should be individualized, based on various factors including age, clinical status, nutritional status, severity of background illness, and concurrent use of certain medications (e.g., corticosteroids).

Management of hyperglycemia in critically ill patients

Summary box

Correction of hyperglycemia in critically ill patients being hospitalized in an ICU setting warrants use of intravenous insulin infusion (Box 7.1)

Box 7.1 Intravenous insulin infusion at a glance (mainly applies to critically ill patients)

Decision to initiate IV insulin

Hyperglycemia in:

- Critically ill patients
- Diabetic ketoacidosis
- Hyperosmolar, non-ketotic hyperglycemia
- Shock
- Occasionally perioperative care
- Myocardial infarction
- After cardiac surgery
- Very high insulin needs and unstable plasma glucose values

Insulin type

- Human regular insulin

Insulin concentration

- 1–10 IU per 10 ml N/S (0.9% NaCl)
- Higher if fluid restriction or very high insulin needs. Use of electromechanical pump is preferable

(Continued)

Box 7.1 (*Continued*)**Initial insulin IV bolus**

- Number of units = BG (mg/dl)/70. No bolus if BG <200 mg/dl (11.1 mmol/L)

Infusion rate

- Start with 1 IU per hour or with 50% of previous total insulin requirements
- If BG >250 mg/dl, calculate initial IIR using the formula:
IIR = BG (mg/dl)/70

Infusion rate adjustment

- Use predefined algorithm

Glucose infusion

- Administer glucose at 5–10 g/h depending on patient's condition and fluid requirements

BG monitoring

- Measure capillary, arterial, or venous BG hourly
- Arterial blood gas analyzers or laboratory analyzers are preferred. If portable glucose meters are used, cross-check extreme BG values
- If BG stable for >3–4 h, check every 2–4 h

Potassium

- Monitor plasma K⁺ every 4–6 h initially, then, if stable, every 12 h

Transition to SC insulin therapy

- Administer SC insulin 1–2 h before stopping IV infusion

BG, blood glucose; IIR, insulin infusion rate; N/S, normal saline.

The insulin requirements of critically ill patients are usually high or change rapidly, and patients often suffer from conditions that render the subcutaneous route of insulin administration problematic, including decreased perfusion of subcutaneous tissue, extensive cutaneous edema, and the need for support with inotropic agents. Obviously, IV administration of insulin surmounts

difficulties associated with its absorption from subcutaneous tissue, while at the same time providing advantages in flexible dose adjustments according to each patient's needs. Furthermore, the ICU is an "ideal" setting for IV insulin therapy as blood glucose monitoring can be instituted and performed on a regular basis (usually once or twice per hour), intravenous lines can be properly inserted and maintained, and infusion systems can accurately deliver insulin volumes hourly, even at very low rates. Frequent monitoring of electrolytes (especially potassium) in the ICU constitutes an important component of patient management as well.

The decision to initiate insulin infusion therapy depends on several factors. A glycemic threshold for starting intravenous insulin is usually pre-established depending on the glycemic target range of each individual patient. As a general rule, when the upper limit of the target range is approached, insulin is started. In critically ill patients with a history of Type 1 diabetes, insulin infusion should be immediately initiated, regardless of plasma glucose value, since insulin-deficient individuals would, otherwise, rapidly develop diabetic ketoacidosis. The same principle applies for individuals with Type 2 diabetes treated with insulin before their admission, although they are less prone to ketoacidosis than Type 1 diabetics.

Human regular insulin should be used for intravenous infusion. There is no advantage of using rapid-acting insulin analogs for that purpose. Insulin is usually added to normal saline solution at 1–10 units per 10 ml. More concentrated solutions may be prepared if high fluid volume load is to be avoided, or in patients with increased insulin needs. An electromechanical infusion pump with a built-in battery supply is the preferred system for safe and accurate infusion. An initial IV insulin bolus is sometimes used if blood glucose value is substantially higher than the upper limit of the accepted glucose target range. As a rule of thumb, the number of insulin units that should be initially administered, as a bolus, can be calculated as the ratio of plasma glucose value (in mg/dl) divided by 70.¹⁶ Infusion rate should be generally started at 1 IU/h or 0.02 IU/kg per hour and adjusted subsequently according to the results of frequent glucose monitoring. In previously insulin-treated patients, the initial infusion rate may be calculated according to their previous total daily insulin dose. Basal insulin requirements are usually 50% of the total insulin needs. Thus, a critically ill patient who was previously treated with 80 IU of insulin daily has ~40 IU of basal insulin requirements and his intravenous insulin infusion may be

started at $40/24 = 1.7$ IU/h. Higher infusion rates can be used if blood glucose is very high. As a rule of thumb, the initial insulin infusion rate (in IU /h) may be calculated by dividing plasma glucose value (in mg/dl) by 70.¹⁶ Thus, in a person with plasma glucose of 450 mg/dl (25 mmol/L), intravenous insulin infusion may be started at 6.4 IU /h. According to the protocol in use, this value can be rounded to 6.0 IU/h. Slower infusion rates should be used for patients with renal or hepatic failure.

Whatever the starting infusion rate, quick adjustment is the cornerstone of successful therapy. Several algorithms for insulin infusion rate adjustments have been designed to be used by the nursing staff of ICUs.^{12,13,16–20} There are no studies comparing the performance of different insulin infusion protocols. Hence, the application of a certain algorithm should be based on each institution's experience and adaptation to the individual hospital environment. Nurses should be carefully trained in how to use these algorithms. It should be clearly explained that insulin requirements may differ widely between individuals but may also change dramatically for the same patient during the course of his/her treatment. It should also be emphasized that rate adjustment depends not only on the obtained blood glucose level at a given moment but, equally important, on the rate of change of blood glucose level over time, especially between the previous measurement and the current one. Thus, if blood glucose is measured at 275 mg/dl (15.5 mmol/L), a value well above the usual glycemic target range (140–180 mg/dl [7.8–10 mmol/L]), the infusion rate should be increased if the previous measurement was similar or lower to the current one, but should *not* be increased, and should even sometimes be decreased, if the previously measured blood glucose was well above the current value (e.g., >400 mg/dl [22.2 mmol/L]).

Blood glucose monitoring of the critically ill patient with hyperglycemia treated with insulin infusion should be performed hourly. When blood glucose levels stabilize within the target range for at least 4–6 hours, then measurements may be obtained every 2–4 hours.

Caution should be paid to the performance of bedside glucose measurements, since the accuracy of certain portable glucometers in the ICU setting has been questioned.¹⁵ Several factors may contribute to this inaccuracy. For example, it is known that some glucose meters are affected by the PO₂ concentration, resulting in meter-reported (artificially) lower glucose concentrations in capillary blood than in venous or arterial blood in cases of poor perfusion.²¹ In addition, low hematocrit values (usually <25%) are also

known to cause spuriously low capillary glucose measurements. We recommend blood samples for glucose measurement to be obtained by means of arterial catheters whenever possible. Arterial blood gas analyzers or laboratory analyzers should be preferred over portable glucose meters. If, however, a portable glucose meter is used, cross-checking of extreme blood glucose measurements with a centrally performed biochemical measurement is strongly recommended.

Concurrent to infused insulin, enough glucose should be provided in order to prevent ketosis and avoid hypoglycemia. Most experts recommend 5–10 g/h.²² Glucose infusion should be avoided if blood glucose levels are above 250 mg/dl (14.4 mmol/L).

When transition from IV insulin infusion treatment to subcutaneous insulin has been decided, subcutaneous injection should always be performed 1–2 hours (depending on the insulin preparation) before interruption of IV insulin, in order to allow enough time for insulin absorption from the injection site. This is especially important for patients with Type 1 diabetes who completely lack endogenous insulin. An intermediate/long-acting insulin preparation should be started (NPH, glargine, or detemir) in order to meet the patient's basal insulin requirements. Short-acting insulin (human regular, lispro, aspart or glulisine) should be used to cover prandial needs or for correction of high blood glucose values.

Management of the non-critically ill hospitalized patient with hyperglycemia

In the present section, we review the management of hyperglycemia in the general medical in-hospital ward. Perioperative management of hyperglycemia will be discussed separately in the next section.

Summary box

The following issues should be taken into account when implementing treatment of hyperglycemia for a hospitalized, non-critically ill patient (Figure 7.1):

- Previous treatment for hyperglycemia (if known diabetic)
- Type of diabetes
- Reason for hospitalization
- Previous quality of glycemic control
- Presenting plasma glucose value
- Nutritional status and in-hospital diet

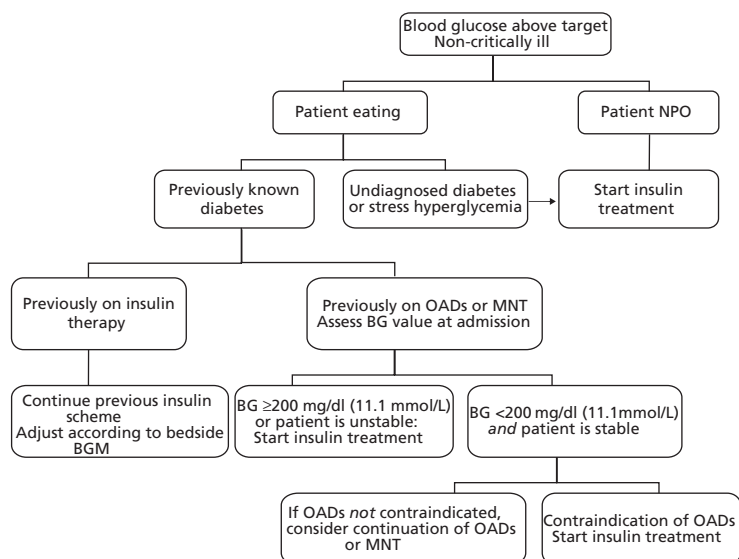


Figure 7.1 Suggested algorithm for in-hospital management of hyperglycemia in non-critically ill patients. No absolute rules exist and individualization is required. BG: blood glucose; BGM: blood glucose monitoring; OAD: oral antidiabetic agent; NPO: nothing per os; MNT: medical nutrition therapy.

Treatment with oral antidiabetic agents (OADs)

Summary box

OADs are usually reserved for stable, able to eat, well-controlled patients with known diabetes who were previously treated successfully with these agents and have no contraindication to their use. Hence, orally administered agents have a limited role in the inpatient setting

The major disadvantages of in-hospital OAD use are described in Box 7.2. Special caution should be taken regarding contraindications to OAD use, frequently present in hospitalized patients. As an example, metformin, the most widely prescribed OAD, is contraindicated in conditions predisposing to lactic acidosis and/or before

Box 7.2 Disadvantages of in-hospital OAD use

Non-flexibility

Inability to titrate rapidly

Limited glucose-lowering capacity

Long half-life (for most agents)

Interaction with other drugs

Class-specific side effects and/or contraindications:

- Sulfonylureas
 - Inhibition of cardiac ischemic preconditioning
 - Prolonged hypoglycemia
- Metformin
 - Predisposition to lactic acidosis if:
 - Renal failure
 - Severe heart failure
 - Exacerbation of chronic pulmonary disease
 - Tissue hypoxia
 - Need for radiographic contrast studies
 - Nausea, diarrhea, and decreased appetite
- Thiazolidinediones
 - Fluid retention
 - Heart failure
 - Drop in hematocrit
 - Rosiglitazone: may predispose to ischemic heart disease
- Incretin-based therapies
 - Limited experience
 - Nausea and vomiting (incretin mimetics)
 - Some concern for pancreatitis

radiographic contrast studies. Such conditions, however, are often present in patients being hospitalized for various reasons. The major categories of OADs—insulin secretagogues (sulfonylureas and glitinides), biguanides, thiazolidinediones, and incretin-based drugs (including the subcutaneously administered incretin mimetics)—have not been systematically studied for inpatient use. In selected, stable patients who were previously treated and well controlled on OADs, such treatment may be continued in the hospital if blood glucose is not significantly disrupted.

Treatment with insulin

Insulin therapy is usually the preferred way to control hyperglycemia in hospitals. The basic principle of any insulin treatment is to “mimic” the physiological insulin secretion pattern, providing supplementation of both basal and prandial insulin requirements.²³ In Type 1 diabetes patients (characterized by complete insulin deficiency), this goal is achieved by multiple daily injection (MDI) insulin regimens or with use of continuous subcutaneous insulin-delivering systems (often named “insulin pumps”), whereas in Type 2 diabetes patients (characterized by relative and partial lack of insulin), simpler insulin regimens may also be used (Figure 7.2).

Summary box

Two main questions have to be addressed when implementing insulin treatment in a hospitalized patient:

- Is the patient eating?
- Had the patient been using insulin before admission?

Patients who are eating and had been using insulin before admission

These patients may usually continue their outpatient insulin regimen. In-hospital insulin requirements may, however, differ substantially. Acute illness, reduced physical activity, and the use of certain medications (such as glucocorticoids) increase insulin demands. On the other hand, hospitalized patients often have decreased dietary intake, thus requiring less insulin. Bedside glucose monitoring with a portable meter should be performed regularly (usually before meals) and, if required, adjustments of insulin doses should be prescribed, based on obtained blood glucose values.

Patients previously receiving basal insulin combined with OADs, for whom OADs are contraindicated during hospitalization, should continue their basal insulin treatment and a short-acting insulin injection before meals should be introduced in order to cover prandial insulin requirements (see below).

Patients who are eating but had not been using insulin before admission

These patients may start insulin therapy as follows:

- *Basal insulin requirements* should be covered using intermediate- or long-acting insulin. One injection of a long-acting insulin

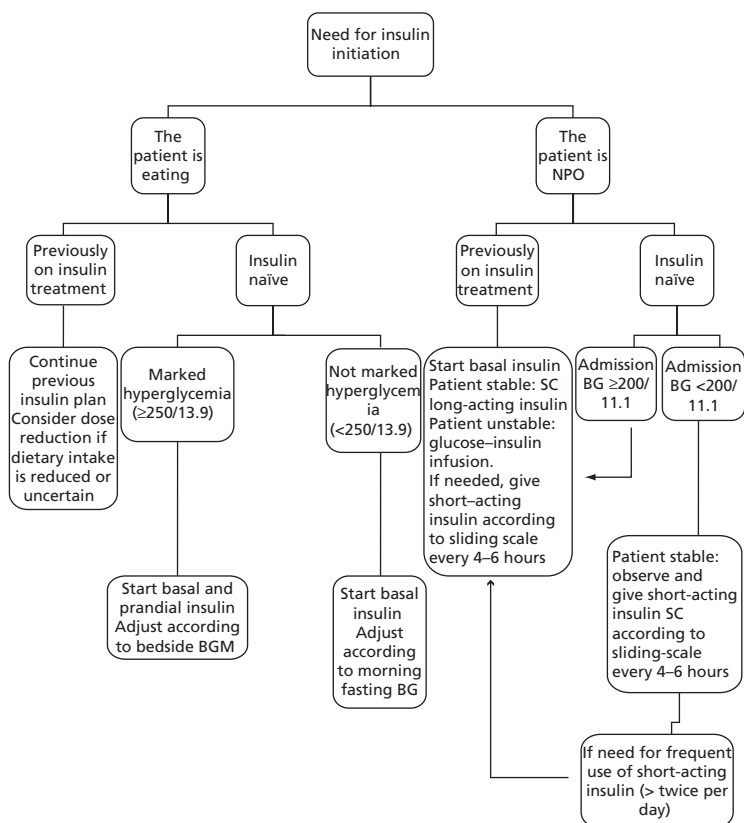


Figure 7.2 Suggested algorithm for initiation of insulin in hospitalized patients. No absolute rules exist and individualization is required. All BG values are presented as mg/dl / mmol/L. NPO: nothing per os, BG: blood glucose, BGM: blood glucose monitoring.

analog (glargine/detemir) in the evening is usually enough for patients with Type 2 diabetes. Patients with Type 1 diabetes may need two injections of insulin detemir (one in the morning and one in the evening). Two NPH insulin injections (one in the morning and one in the evening) are required in order to fully cover basal insulin needs in both types of diabetes.

A starting dose of 0.2IU/kg body weight is generally recommended (Box 7.3). Adjustment of basal insulin dose may be performed every 2–3 days, based on morning fasting plasma glucose values (Box 7.3).

Box 7.3 Algorithm for initiation and titration of basal insulin in hospitalized patients

Starting dose: 0.2 IU/kg body weight

- If fasting plasma glucose >250 mg/dl (13.9 mmol/L): increase by 20%
- Renal failure or hepatic failure: decrease by 20%

Titration: adjust every 2–3 days, based on morning fasting plasma glucose value. If two NPH insulin injections are used, adjust as above for the evening dose, and adjust the morning dose based on pre-dinner plasma glucose value.

Above target:

- +1–30 mg/dl (1.7 mmol/L): add 2 units
- +31–60 mg/dl (1.71–3.3 mmol/L): add 4 units
- +61–90 mg/dl (3.31–5 mmol/L): add 6 units
- +91–120 mg/dl (5.01–6.7 mmol/L): add 8 units
- +121–150 mg/dl (6.71–8.3 mmol/L): add 10 units

On target: keep the dose stable

Below target: –(1–30) mg/dl (1.7 mmol/L), subtract 2 units

- Hypoglycemia: subtract 3–8 units depending on the severity and possible cause of glucose decline

In some patients with Type 2 diabetes and mild hyperglycemia, basal insulin therapy may be sufficient to restore both fasting and postprandial glucose levels to within the desirable target range. This is due to restoration of glucose toxicity and improvement of insulin secretion from the β -cells.

- Prandial insulin should be started when postprandial blood glucose levels (usually measured 2 hours after meals) exceed 180 mg/dl (10 mmol/L) or pre-lunch/pre-dinner values exceed 140–150 mg/dl (7.8–1.3 mmol/L). Prandial insulin injections should be started from the beginning, along with basal insulin, in patients with Type 1 diabetes, or if marked hyperglycemia (≥ 250 mg/dl [13.9 mmol/L]) is present at hospital admission.

A short-acting insulin (either human regular insulin or a rapid-acting analog: lispro, aspart, or glulisine) should be used. Regular human insulin should ideally be given 30–45 minutes before meals.²³ In the busy hospital setting, it is often difficult to ensure that the right timing between insulin injection and meal consumption is followed. From this point of view, insulin analogs

may offer an advantage over human insulin, since they can be injected immediately before or even immediately after meals. Indeed, one (small) recent study in non-critically ill patients showed that combining insulin glargine at bedtime with insulin glulisine before meals resulted in better glycemic control (with similar rates of hypoglycemia) than when glargine was combined with human regular insulin.²⁴ Another (small) clinical study, however, compared the combination of detemir (once daily)/aspart (before meals) to a split-mixed regimen with NPH and regular insulin, given twice daily, and found no difference in glycemic control and hypoglycemia between groups.²⁵

The dose of prandial insulin is highly individualized. A safe starting dose is usually 4 IU of insulin before each meal, assuming that the meal contains ~60 g of carbohydrates (1 IU per 15 g of carbohydrates). Insulin-resistant patients may need higher doses. Additional units should be added when preprandial blood glucose value exceeds the glycemic target (<140 mg/dl [7.8 mmol/L]). One additional insulin unit may be added for every 40 mg/dl (2.8 mmol/L) increase in preprandial blood glucose. Insulin-resistant patients may need additional correction units (e.g., 2–4 IU per 40 mg/dl (2.8 mmol/L) increase). A sliding scale for preprandial insulin administration is described in Table 7.1a.

It should be emphasized that the doses depicted in Table 7.1a are only indicative. Many patients, especially those with Type 2 diabetes, may need higher doses. On the other hand, patients with renal failure or severe hepatic insufficiency may need less insulin. Prandial insulin dose is adjusted (ideally) on the basis of plasma glucose value two hours postprandially or (if this is not available) before the next meal. When adjusting prandial insulin, the patient should be asked whether all or part of the meal was consumed or if any additional food and/or soft drink were consumed.

- In some cases, stable patients with a regular diet can be treated with a premixed insulin preparation, given usually before breakfast and dinner. Such a regimen is simpler and easier to administer but, on the other hand, it lacks flexibility since basal/prandial insulins are premixed in a fixed ratio (usually 70% of intermediate acting insulin with 30% human regular insulin or a rapid-acting analog). If such a regimen is administered, additional prandial insulin may be needed, especially before lunch.

Table 7.1a Sliding scale for initiation of preprandial subcutaneous insulin in hospitalized patients eating a regular meal containing approximately 60g carbohydrate

Preprandial plasma glucose (mg/dl [mmol/L])		Short-acting insulin dose (IU)
<140	(7.8)	No insulin*
141–180	(7.8–10.0)	4–5
181–220	(10.0–12.2)	5–6
221–260	(12.2–14.4)	6–7
261–300†	(14.4–16.7)	7–8

The insulin doses proposed in this table are indications only. Individualization is most important. Consider initiating with a higher (by 20%) dose in patients with BMI >30 kg/m² or those receiving glucocorticoids. Consider a lower dose in cases of renal failure, hepatic failure, or/and the elderly.

If, despite the use of the sliding scale, the next 2 blood glucose measurements (ideally checked 2 h postprandially) are higher than desirable, upgrade the sliding scale by increasing all insulin doses by 1 unit for every 40 mg/dl (2.2 mmol/L) above target.

*Insulin should still be administered in patients with Type 1 diabetes.

†If plasma glucose >300 mg/dl (16.7 mmol/L), delay food and administer 5–6 IU of human regular insulin as a bolus IV, in order to quickly correct blood glucose. Re-measure blood glucose in 45 min and if <300 mg/dl (16.7 mmol/L) proceed as above. If blood glucose still >300 mg/dl (16.7 mmol/L), repeat bolus IV insulin or consider the administration of continuous insulin infusion.

Patients for whom per os feeding is stopped

These patients represent a distinct group. Treatment of hyperglycemia should be extremely careful in this situation, since these patients are prone to develop hypoglycemia due to their limited carbohydrate intake.

By definition, patients who are unable to eat need only basal insulin supplementation. Three approaches may be implemented for this purpose:

- *Subcutaneous basal insulin* may be administered as described for patients who can eat. The subcutaneous approach is simple and easy to follow in the general care setting. For unstable patients, however, it might produce unpredictable blood insulin levels, leading to undesirable hyper- or hypoglycemia. Dose adjustments are less flexible and should be performed daily, as previously described. Additional human regular insulin may be given every 4–6 hours, according to sliding scale in Table 7.1-b.

Table 7.1b Sliding scale for correctional subcutaneous insulin administration in non-critically ill, hospitalized patients who are NPO*

Plasma glucose (mg/dl [mmol/L])		Short-acting insulin dose (IU)
<140	(4.4)	No insulin
141–180	(7.8–10.0)	1–2
181–220	(10.0–12.2)	2–3
221–260	(12.2–14.4)	3–4
261–300 [†]	(14.4–16.7)	4–5

The proposed insulin doses are indications only. Individualization is most important. Higher doses may be required in obese patients and those with high levels of insulin resistance.

If, despite the use of the sliding scale, the next 2 blood glucose measurements (checked 4–6 hours after each injection) are higher than desirable, upgrade the sliding scale by increasing all insulin doses by 1 unit for every 40 mg/dl (2.2 mmol/L) above target.

*Basal insulin requirements should be covered with SC long-acting insulin or human regular insulin infused within a glucose–insulin–potassium solution. If insulin infusion is administered via a separate line, correction with SC human regular insulin is not indicated.

[†]If blood glucose >300 mg/dl (16.7 mmol/L), part of the additional insulin (40–60%) may be given as an IV bolus. In this case, blood glucose should be re-checked after 2 hours. If blood glucose is still above 300 mg/dl (16.7 mmol/L) IV bolus may be repeated. If blood glucose consistently remains above 300 mg/dl (16.7 mmol/L), continuous insulin infusion via a separate line should be considered.

PG: plasma glucose; NPO: nothing per os.

- *Glucose–insulin infusion* In patients receiving 24-hour dextrose IV infusion, human regular insulin may be added within the dextrose solution, together with the electrolytes needed. This approach gives the possibility of more flexible adjustments in insulin dose. Furthermore, in unstable patients, IV insulin administration bypasses the need for subcutaneous absorption, which can be uncertain in cutaneous hypoperfusion states. On the other hand, continuity and accuracy of infusion should be ascertained, otherwise the patient might rapidly become insulin-depleted or insulin over-treated, both potentially dangerous situations. Another limitation is the need to mix up a new infusion vial (or bag) every time an adjustment in insulin dose becomes necessary. Furthermore, the fluid volume supplied may also need frequent

adjustments, making the provided insulin dose calculations even more complicated.

A basic recipe for a glucose–insulin–potassium infusion (*GIK regimen*) has been previously described:^{26,27} 500 ml of 10% dextrose solution should initially contain 15 IU of regular insulin and 10 mmol of potassium chloride and be infused over 5 hours.^{10,26,27} According to the basic recipe,¹⁰ blood glucose should be checked initially every hour, and the insulin concentration of the bag/vial should be changed accordingly (e.g., the bag should be changed to contain 20 IU of insulin if blood glucose >200 mg/dl [11.1 mmol/L], or 10 IU if BG <110 mg/dl [6.1 mmol/L]).

In our hospital we use a different, easy to perform, protocol: the patient receives a 24-hour glucose infusion (5–10%) with added electrolytes as required. The infusion contains 8–16 IU /1000 ml of human regular insulin. The higher range of concentration is used in patients with higher insulin requirements. Blood glucose is checked every 4–6 hours and additional insulin boluses (Table 7.1b) are given subcutaneously (the patient should have stable vital signs). If blood glucose is too high (≥ 300 mg/dl [16.7 mmol/L]), additional insulin may be given as an IV bolus. In this case, blood glucose should be re-checked after 2 hours. This protocol may be used pre- or postoperatively as well. Our experience over more than two decades has shown that this system is effective, simple, and safe.

- *A separate insulin infusion* as described in the previous section “Management of hyperglycemia in critically ill patients.” This approach is preferred for most unstable patients with high insulin requirements. In the general medical setting, however, such an approach is less feasible, since proper and close monitoring of all parameters associated with continuous insulin infusion is often difficult to implement. Although in the ICU setting intravenous lines and infusion systems are carefully and repeatedly checked, this is not always the case in the general medical ward. Of note is that clinical trials examining the effect of separate insulin infusion on several outcomes in patients with diabetes have all been performed in the ICU setting.^{12,13,16,18–20}

In some patients exhibiting mild hyperglycemia (<200 mg/dl [11.1 mmol/L]), observation of blood glucose only may be instituted, without the implementation of basal insulin. Small-dose corrections with short-acting insulin every 4–6 hours, according to a sliding scale (Table 7.1b), may be prescribed. If large and/or fre-

quent corrections are needed, however, basal insulin should be started as described above. This approach is contraindicated in Type 1 diabetes.

Perioperative management of hyperglycemia

Hyperglycemia during the perioperative period often contributes to possible adverse outcomes of surgery as it promotes infections, electrolyte abnormalities, dehydration, acidosis, poor wound healing, and thrombotic complications.²⁸ A recent retrospective study examining 2090 general and vascular surgery patients suggested that postoperative hyperglycemia may be the most important risk factor for surgical site infection.²⁹ The glycemic targets proposed for the treatment of in-hospital hyperglycemia also apply to patients who undergo surgery. No specific guidelines exist, however, regarding the perioperative management of hyperglycemia. Hence, clinical experience, together with some evidence derived mainly from retrospective studies and studies in the ICU setting, guide the clinical decisions.

Summary box

The perioperative management of a patient with hyperglycemia depends on the following factors:

- Type of surgery (major versus minor)
- Quality of previous glycemic control
- Type of diabetes (Type 1 versus Type 2)
- Type of previous antidiabetic treatment (diet alone, and/or oral agents, and/or insulin)

Type of surgery

Major operations are expected to produce significant metabolic decompensation due to large increases in counter-regulatory hormone secretion (particularly catecholamines and cortisol), prolonged bed rest, possible volume depletion, and food deprivation. The above changes result in peripheral insulin resistance, increased hepatic glucose production, impaired insulin secretion, and fat and protein breakdown, which promote hyperglycemia and in some cases even ketosis.³⁰

Quality of previous glycemic control

Previous control of glycemia strongly predicts the blood glucose levels before surgery. It is generally recommended to obtain an HbA_{1c} value during the overall preoperative assessment of a diabetic patient.^{9,10} A high HbA_{1c} (especially if >8%) combined with blood glucose levels above 180mg/dl (10mmol/L) indicates that preoperative blood glucose control is poor and that marked glucose decompensation may be expected during and after surgery.

Type of diabetes

It should always be kept in mind that patients with Type 1 diabetes have absolute insulin deficiency (rendering them prone to diabetic ketoacidosis) and their blood glucose levels, even if well controlled, may often fluctuate significantly. Therefore, hypoglycemia is a frequent (almost everyday) phenomenon in these patients. Insulin should never be stopped in Type 1 diabetic patients. Self-knowledge of diabetes by these patients is an important feature that should be taken into account when making treatment decisions.

Patients with Type 2 diabetes represent a heterogeneous group. Their perioperative management depends mainly on the type of previous antidiabetic treatment and the level of previous glycemic control.

Type of previous treatment

Patients receiving insulin usually maintain their treatment plan until surgery. Patients controlled on diet alone or those receiving OADs having good glycemic control may retain their treatment until the evening before the operating day. A common problem lies in patients receiving high doses of OAD combinations while maintaining poor glycemic control. These patients need to start insulin treatment and, if possible, insulin should be initiated 10–14 days before surgery in order to allow sufficient time for hyperglycemia to improve.

Preoperative period management

A proposed algorithm for the preoperative management of hyperglycemia is depicted in Figure 7.3.

Patients with reasonably good previous glycemic control (HbA_{1c} <8% and/or plasma glucose values <180mg/dl [10mmol/L]) who undergo minor surgery do not need specific therapy. They can

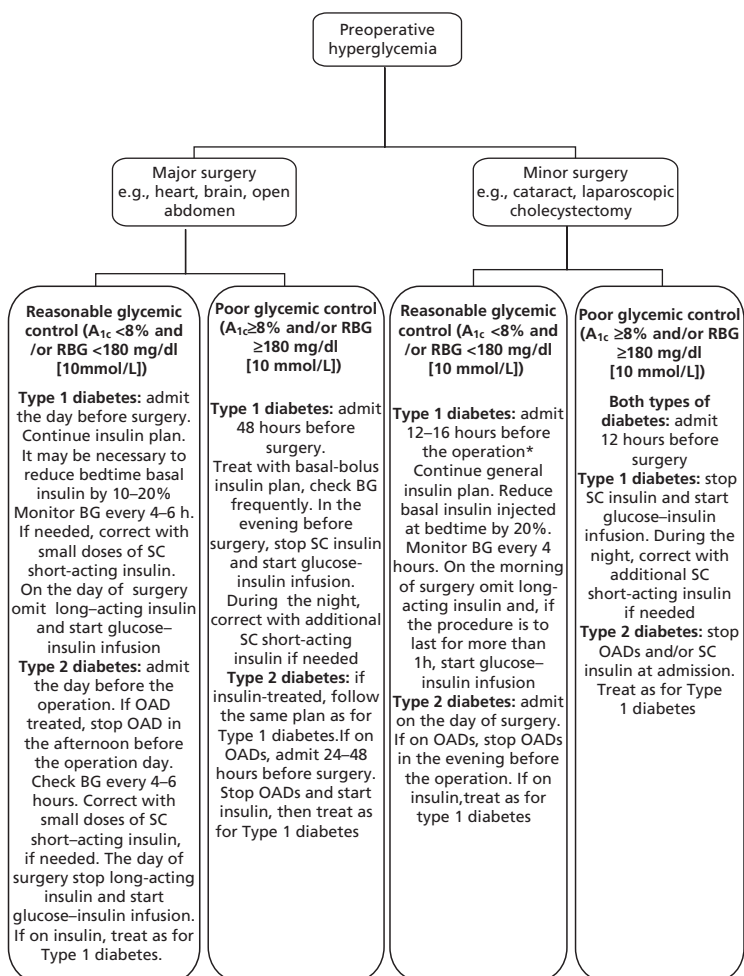


Figure 7.3 Suggested algorithm for preoperative management of hyperglycemia. No absolute rules exist and individualization is required.

*Selected patients with Type 1 diabetes and excellent glycemic control may be admitted on the day of operation. BG: blood glucose; GIK: glucose–insulin–potassium; OAD: oral antidiabetic drugs; RBG: random blood glucose.

continue their usual treatment until the day of the surgery. All OADs and long-acting insulin (only for Type 2 diabetic patients) should be withheld on the day of the operation. As an exception, for patients with Type 1 diabetes and an $HbA_{1c} < 8\%$ but unstable blood glucose values and/or frequent hypoglycemic events, it might be preferable to admit 12 hours before surgery and frequently monitor blood glucose in order to avoid large fluctuations of glycemic levels.

If major surgery is planned, admission is usually required for patients on insulin treatment 12–24 hours before the procedure. Patients with Type 1 diabetes may continue their usual insulin plan. The bedtime basal insulin dose may be reduced by 10–20%. Frequent blood glucose monitoring should be performed (every 4–6 hours) and additional short-acting insulin should be administered SC, if required, according to a sliding scale such as the one depicted in Table 7.1b. The same plan is recommended for insulin-treated Type 2 diabetic patients. As mentioned above, OADs should be stopped in the afternoon before operation. The last dose of sulfonylureas (glimepiride, gliclazide, glibenclamide, or glipizide) should be taken at least 18 hours before surgery. In the morning of the operation SC insulin should be withheld and a glucose–insulin infusion started, as described previously. The last OAD dose (including sulfonylureas) should be taken no later than at lunch of the day before surgery.

Patients with poor control of glycemia ($HbA_{1c} \geq 8\%$ and/or fasting plasma glucose ≥ 180 mg/dl [10 mmol/L]) represent a major problem in diabetes preoperative care. This group is comprised of both patients with known diabetes as well as recently (often on the occasion of the scheduled surgery) diagnosed patients with marked hyperglycemia. Additional time should be given to these patients in order to improve their glycemia before admission for surgery. The operation may even be postponed for a few days in order to decrease blood glucose levels. If, however, the patient is still markedly hyperglycemic, or surgery cannot be postponed, it might be wise to recommend admission 24–48 hours before a major operation or 12 hours before a minor one. Insulin should be initiated in a basal-bolus scheme, as described earlier in this chapter (see “Treatment with insulin”). In the evening before a minor surgical procedure, only basal insulin (especially in Type 1 diabetes) and/or small correctional doses of short-acting insulin SC by sliding scale (see Table 7.1) need be administered in order to achieve acceptable

blood glucose values the next morning. In the evening before major surgery, however, it might be preferable to stop SC insulin and administer a glucose–insulin infusion, while at the same time frequently checking blood glucose at the bedside (usually every 4 hours) and injecting additional short-acting insulin SC by sliding scale as required (see Table 7.1). The preparation of a glucose–insulin infusion solution has been described earlier in this chapter (see “Treatment with insulin”).

Intraoperative period management

All patients with Type 1 diabetes, and many with Type 2 diabetes, require continuous insulin infusion during operation in order to maintain glycemic control. Diet-controlled or small-dose OAD treated patients with Type 2 diabetes maintaining good glycemic control (preoperative HbA_{1c} <7%) may not require insulin if the surgical procedure is relatively short.

The aim of intraoperative treatment of hyperglycemia is to maintain good glycemic control (avoiding hyperglycemia and hypoglycemia) and prevent other metabolic disturbances (ketosis, fluid depletion, etc.). The key to success is careful and frequent blood glucose monitoring to detect any alterations in glucose control and correct them before they become severe.

In minor surgical procedures of short duration a glucose–insulin infusion is usually sufficient, while additional small doses of insulin may be given as IV bolus, if required. In major operations, a separate insulin infusion, as described earlier in this chapter (see “Management of hyperglycemia in critically ill patients”) may be the preferred approach.

Postoperative period management

During the postoperative period, management of hyperglycemia follows the same principles as for hospitalized patients. If a patient is transferred to the ICU, insulin infusion therapy via a separate line is usually the treatment of choice, as described in the section “Management of hyperglycemia in critically ill patients.” In general surgery care, the treatment should aim at quick and safe restoration of the previous antidiabetic therapy plan (if successful) or (if not) a new type of treatment, as described in section “Management of the non-critically ill hospitalized patient with hyperglycemia.”

Treatment of in-hospital hyperglycemia in specific situations

Emergency surgery

It is a common situation that many patients with diabetes who require emergency surgery exhibit markedly increased blood glucose levels, even if they had previously maintained decent glycemic control. In some cases, they may even have diabetic ketoacidosis.

The first priority is to assess glycemic, acid–base, electrolyte, and fluid status, and try to correct any abnormalities before surgery. This is especially critical if acidosis or potassium disturbance are present. In this context, hyperglycemia should be controlled by using insulin infusion, as described in the section “Management of hyperglycemia in critically ill patients.” Surgery should be delayed, if possible, in order to stabilize metabolic status.³¹

Total parenteral nutrition (TPN)

There are no controlled trials examining the best approach for treating hyperglycemia in patients receiving TPN. One option is to add insulin to the TPN, but it may become difficult to assess the required insulin dose. A separate intravenous insulin infusion may be used instead, especially in the ICU setting, and this approach has been reported to achieve glucose target within 24 hours.³² At that time, 70–100% of the calculated dose may be added to the TPN bag while the separate insulin infusion is stopped.³²

Use of glucocorticoids

Glucocorticoids induce hyperglycemia by inhibiting glucose uptake into muscle, by increasing hepatic glucose production, and by directly inhibiting insulin secretion.^{33,34} The first mechanism seems to prevail, leading to the well-recognized predominant increase in postprandial glycemia.³³ Hyperglycemia caused by glucocorticoid use may be severe. The best predictors of severity are family history of diabetes, increasing age, and glucocorticoid dose.⁴

Although insulin resistance seems to be the major mechanism driving high glucose levels in individuals receiving glucocorticoids, insulin sensitizers (especially thiazolidinediones) are not appropriate for the management of in-hospital acute hyperglycemia, due to the fact that their antihyperglycemic effects take a long time to appear. Therefore, insulin is recommended in this situation.⁴

Although no relevant clinical trials exist, given that glucocorticoids exert their hyperglycemic effect mainly on postprandial glucose, the insulin treatment plan should emphasize the use of prandial over basal insulin. Since glucocorticoids are usually administered in the morning, pre-breakfast and pre-lunch SC insulin administration will probably cover most of the patient's insulin requirements. In diabetic patients previously treated with insulin, additional prandial insulin, especially before breakfast and lunch (if steroids are given in the morning), is often needed. In insulin-naïve patients, one NPH insulin injection in the morning, combined with human regular insulin (or a rapid-acting analog) injected before lunch (higher dose) and dinner (lower dose), is usually a reasonable choice. A 30:70 premixed insulin injection before breakfast and a 50:50 premixed insulin injection before lunch is a possible alternative, frequently used in clinical practice. Caution should be paid if pre-dinner or bedtime insulin is injected, as glucose values are expected to drop during the night (especially if no glucocorticoids are given at that time).

For patients who are not eating, those who are critically ill, or if high-dose glucocorticoid therapy is administered (often given intravenously), an intravenous insulin infusion is more appropriate. It should be kept in mind, however, that infusion rates should be expected to increase substantially after meals. The insulin requirements are extremely difficult to predict. If an insulin infusion is used, it is possible to achieve required insulin dosing more quickly.³⁵

Case studies

Case 7.1

A 71-year-old female suffering from severe coronary heart disease has been scheduled to undergo coronary artery bypass grafting. The patient has had a history of Type 2 diabetes for 12 years and her latest antidiabetic treatment has included glimepiride 6mg daily (taken before breakfast) and metformin 1700mg b.i.d. (850mg at lunch and 850mg at dinner). Her HbA_{1c}, measured during her overall preoperative evaluation (one week before surgery), was 9.5% and her fasting plasma glucose (FPG) 298mg/dl (16.6mmol/L). Her BMI was 29kg/m² (body weight: 78kg). Plasma creatinine and liver function tests were normal.

How should this patient's hyperglycemia be managed preoperatively?

Glycemic control for this patient was poor, well above the generally recommended target of 7.0%. After the preoperative evaluation, a consultation by a diabetologist was requested, basal insulin was recommended and the patient started insulin glargine, 10IU q.d. at bedtime, in combination with the oral antidiabetic drugs already being received. A program for self-titration of basal insulin, based on morning's fasting capillary glucose self-measurements, was explained to the patient. Admission was scheduled at 24 hours before surgery.

In the morning of admission, the patient's fasting plasma glucose was 224mg/dl (12.4mmol/L), while insulin glargine was titrated up to 22IU. According to the patient's glucose diary, 2-h postprandial blood glucose (BG) during the previous week ranged between 230 and 280mg/dl (12.8–15.6mmol/L).

Glimepiride and metformin were stopped and 6IU of human regular insulin (HRI) were administered 30min before breakfast (containing ~60g of carbohydrates [CHO]) according to the sliding scale shown in Table 7.1a. Pre-lunch capillary BG was 214mg/dl (11.9mmol/L) and 8IU HRI were injected before lunch (containing ~60g of CHO). The corresponding dose in Table 7.1a was increased by 2IU because the pre-breakfast use of the scale (6IU) failed to reach target (pre-lunch value <140mg/dl/7.8mmol/L) by 74mg/dl (4.1mmol/L). Thus the preprandial insulin sliding scale for this patient should be more intense than the one shown in Table 7.1a by (at least) 2IU per row. Pre-dinner capillary BG was 154mg/dl (8.6mmol/L), a value very close to target. A light dinner (30g CHO) was then offered and 4IU of HRI were given SC (half the dose of the [intensified] sliding scale, due to the low CHO content of the meal). Four hours later (at 22.00), capillary BG measured 145mg/dl (8.1mmol/L).

Since this patient exhibited poor glycemic control before admission and major surgery had been scheduled for early next morning (at 07.00), a glucose–insulin infusion was started (1000ml dextrose in water [D/W] 5% + 16IU HIR + 20mEq K⁺) at 60ml/h. A new capillary blood test at 04.00 showed 195mg/dl (10.8mmol/L). Two more IU of HRI were injected SC, according to the sliding scale shown in Table 7.1b (correction scale). At 07.00 (the time just before the operation), capillary BG measured 139mg/dl (7.7mmol/L). No further action was taken.

The patient was operated successfully and remained in the ICU for 72 hours postoperatively. During her stay in the ICU, hyperglycemia was managed by continuous insulin infusion via a separate IV line. The patient was transferred to general care in the afternoon of the third postoperative day, still receiving an insulin infusion at a rate of 3 IU/h. Her BG when she entered the cardiovascular surgery department measured 156 mg/dl (8.7 mmol/L). She was prescribed a diet of ~1600 Kcal/50% CHO daily.

How should her blood glucose be further managed?

The patient should now be transferred to a subcutaneous insulin regimen. Total insulin requirements may be estimated on the basis of her latest insulin infusion rate ($3 \text{ IU/h} \times 24 = 72 \text{ IU/24 h}$). However, insulin requirements are expected to diminish gradually as the patient recovers from the severe stress induced by this major operation. In addition, food intake might be unpredictable during the first days after major surgery.

Subcutaneous basal insulin supplementation with a long-acting insulin analog was recommended, such as insulin glargine or detemir, given once daily at a dose corresponding to 50% of total daily insulin requirements, reduced by 20%: $(72 \times 50\%) - 20\% = 36 - 20\% = 29 \text{ IU}$. Hence, 29 IU of insulin glargine was injected at 20.00 and insulin infusion was interrupted 2 hours later. The next morning, capillary blood glucose measured 115 mg/dl (6.4 mmol/L). Insulin glargine was titrated using the titration algorithm proposed in Box 7.3. Over the next days, if required, additional prandial insulin was given according to the sliding scale in Table 7.1a. The day before discharge, total daily insulin requirements had reached 36 IU, showing a gradual tendency to decline. A combination of insulin glargine (18 IU at bedtime) with glimepiride (2 mg in the morning) and metformin (850 mg b.i.d.) was prescribed.

Case 7.2

A 56-year-old man was admitted to hospital because of acute gastroenteritis. He had had nausea and vomiting, non-bloody diarrhea, abdominal cramps, and high fever for 12 hours before admission. At presentation he was hypotensive (BP 85/45 mmHg) and tachycardic (110/min) and his rectal temperature was 38.8°C (101.8°F). Serum sodium and potassium were measured at 133 mEq/L and 3.2 mEq/L, respectively. Indices of renal and liver function were normal. Occult blood and leukocytes were detected in a stool sample. Blood and

stool cultures were obtained, aggressive fluid and electrolyte replacement was initiated, and IV ciprofloxacin was administered for suspected bacterial gastroenteritis.

The patient had a history of Type 2 diabetes since the age of 46 and was under treatment with metformin, 1000mg b.i.d. and glimepiride (modified release) 90mg q.d. He had a recent HbA_{1c} value of 8.6%. His BMI was 29.5 kg/m² (body weight: 89 kg). On admission, his plasma glucose measured 320mg/dl (17.8mmol/L). Arterial blood gases showed no significant abnormalities.

How should this patient's hyperglycemia be managed?

This patient was unable to eat on admission because of repeated vomiting and abdominal pain, both due to his gastrointestinal tract infection. Despite the fact that he was fasting, blood glucose was remarkably high for two reasons: 1) previous poor glycemic control, and 2) excessive counter-regulatory hormone release resulting from the gastrointestinal tract infection.

Intravenous insulin infusion was preferred over subcutaneous administration because the patient was hypotensive. Hypoperfusion may delay insulin absorption from subcutaneous tissue. Therefore, a 500ml normal saline (N/S) solution containing 50IU of human regular insulin (HRI) was prepared and infusion was started at a rate of 4IU/h (30ml/h) (see Box 7.1) in parallel with aggressive intravenous replacement of fluids and electrolytes.

Intravenous insulin infusion outside the ICU should be performed with extreme caution. An electromechanical pump should be used, if available. If not, the utmost attention should be paid and correct functioning of the infusion system should be regularly checked. Blood glucose should be measured every hour. More dilute insulin solutions are preferred over those with a high insulin concentration (Box 7.1).

One hour after insulin initiation, capillary blood glucose measured 264mg/dl (14.7mmol/L). The infusion rate was kept constant. Five hours later blood glucose was 216 mg/dl (12.0mmol/L). The patient's blood pressure was stabilized at 110/75 mmHg and his pulse rate decreased to 96/min. Body temperature was 38.0°C (100.4°F). Diarrhea continued, vomiting had stopped, but nausea was still present. The insulin infusion rate was decreased to 2IU/h.

Four hours later, blood glucose measured 135 mg/dl (7.5 mmol/L) and the patient's condition was stable. Since insulin requirements

were not high (2IU/h with a tendency to decline) but, at the same time, the patient was not yet able to eat, it was decided to stop insulin infusion via a separate IV line and administer a glucose–insulin infusion, in parallel with the IV fluid/electrolyte correction with N/S solution. The advantage of this approach in the general medical ward is a lower probability of hypoglycemia. Therefore, a D/W 5% solution was prepared, containing 16 IU of HRI and 20 mEq of potassium, for 24-hour infusion. Blood glucose could now be checked every 4 hours. Additional HRI was injected subcutaneously as required (see Table 7.1b), since the patient's blood pressure had been stabilized. Four hours later capillary blood glucose measured 186 mg/dl (10.3 mmol/L) and 2 IU HRI were given subcutaneously, according to a sliding scale (Table 7.1b).

Another 8 hours later, blood glucose measured 147 mg/dl (8.2 mmol/L). Diarrhea was still present but occurred less frequently. The patient was still unable to eat due to nausea and (gradually declining) abdominal pain. During the next few hours, blood glucose levels were kept constant, between 110 and 160 mg/dl (6.1–8.9 mmol/L), without additional insulin.

When the patient started to eat, the glucose–insulin solution was stopped and subcutaneous long-acting insulin was started (18 IU daily, $[0.2 \times \text{body weight}]$), while additional prandial insulin (HRI) was administered as required, according to a sliding scale (Table 7.1a). At discharge, a combination of basal long-acting insulin with metformin and gliclazide (as taken before admission) was prescribed.

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CHAPTER 8

Sick-day rules in diabetes

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Definition

During an acute illness, blood sugar levels usually rise. Illness causes a greater than normal demand for insulin due to the release of stress hormones such as adrenaline (epinephrine), cortisone, and growth hormone. These hormones can be triggered by any kind of stressful condition such as an infection, a cardiovascular or cerebrovascular ischemic event, gastroenteritis, dehydration, etc. As a result of this increase, the body may require more insulin to cope with the increased demand.¹

In diabetic persons, with an already compromised pancreatic insulin reserve (completely absent in Type 1 or diminished in Type 2 diabetes), this increased insulin requirement may not be met unless insulin is given exogenously.² If diabetic control is not attended to under these circumstances it may seriously deteriorate and lead to potentially fatal complications such as diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) (see Chapters 1–3). DKA and HHS are acute, potentially life-threatening complications of diabetes, the occurrence of which can be prevented. Although major advances have improved diabetes care, DKA remains the leading cause of hospitalization, morbidity, and death in young people with Type 1 diabetes (T1DM), and HHS is a serious, potentially lethal complication of diabetes, usually in elderly persons.³

To prevent these complications, it is important to address outpatient educational approaches directed at sick-day management and early identification and treatment of impending DKA or HHS.

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Epidemiology

People with diabetes are no more likely than non-diabetic ones to get sick. However, when they do, their blood sugar levels may deteriorate because of the underlying illness (see “Potential causes” below).

Regarding infections, for example, there are no sufficient data in the literature to substantiate the opinion that diabetic persons, as a whole, have a higher susceptibility to infections. However, some infections are more common and some may have a more severe clinical course and manifest a higher frequency of complications in diabetic persons. These include fungal infections, malignant otitis externa, necrotizing fasciitis, rhinocerebral mucormycosis, and emphysematous cholecystitis. The increased susceptibility that patients with diabetes have to certain infections is due to many factors. The polymorphonuclear neutrophils of diabetic patients have been found to have decreased chemotactic and phagocytic abilities. Furthermore, it seems that the ability of leukocytes to destroy microorganisms after the process of phagocytosis is diminished.

Potential causes

The usual causes involve any kind of a multifactorial etiology for an acute illness—infectious, vascular, metabolic, etc.—that could gradually precipitate a hyperglycemic crisis in a patient with either Type 1 or Type 2 diabetes. The most common etiologies are infectious (respiratory or urinary tract infections, soft tissue infections, gastrointestinal, etc.).⁴ Cardiovascular events are also quite common in elderly individuals. Initiation or increase of corticosteroid therapy is another cause of acute deterioration of diabetic control.⁵

DKA can also be the first manifestation of Type 1 diabetes in previously healthy persons, and this occurrence may be less amenable to prevention.⁴

Diagnosis

There should be a high level of suspicion and awareness among the lay and medical community regarding the early manifestations of hyperglycemic crises, so that appropriate measures can be taken to prevent them.⁶ Early identification and management of impending hyperglycemic crises would definitely help to lower the mortality

of these conditions.⁷ In people with known diabetes this can be relatively straightforward, whereas in persons with the first manifestations of diabetes it may be more complex. The usual symptoms and signs of diabetes (polyuria, polydipsia, and weight loss) should alert patients and their family members to the possibility of an impending deterioration of diabetic status. DKA as an initial manifestation of T1DM may be less amenable to prevention unless there is increased awareness by the lay and medical communities of the symptoms of diabetes and surveillance in high-risk populations, potentially identified by family history or genetic susceptibility.⁴ New bed-wetting in a child without known diabetes or nocturnal enuresis (bed-wetting) in a known Type 1 diabetic child may be the first sign of diabetes or its deterioration and should alert the family.⁸

The risk for T1DM development for the first time cannot be easily predicted and identified, especially by lay people. Clues towards this prediction are highly significant. Thus, studies referenced here^{8,9} found that an incidental finding of a blood glucose level >100 mg/dl (5.6 mmol/L) in a child without a history of DM may denote increased risk for the development of T1DM in the future and should alert physicians and parents towards this possibility, so that DKA may perhaps be anticipated and prevented.

Clinical management

In the case of an acute illness, instructions are individualized and depend on a variety of factors including the type of diabetes, the kind of therapy that the patient receives (pills or insulin, intensity of insulin regimen), the presence of complications, and the type of the acute illness. It is essential that appropriate instructions have been given beforehand so that patients and family on the one hand do not panic and on the other hand do not neglect the condition. It is of paramount importance that treatment of the acute illness is timely, appropriate, and effective. It should always be kept in mind that inappropriate management might lead to significantly poor metabolic control that could increase the risk of an acute complication such as DKA or hyperglycemic hyperosmolar coma.

General instructions for an acute illness at home are (Figure 8.1):¹⁰

1. Insulin should never be omitted (in patients treated with insulin). Even when there is a feeding problem (nausea, vomiting), it is more likely that additional insulin will be needed (due to the

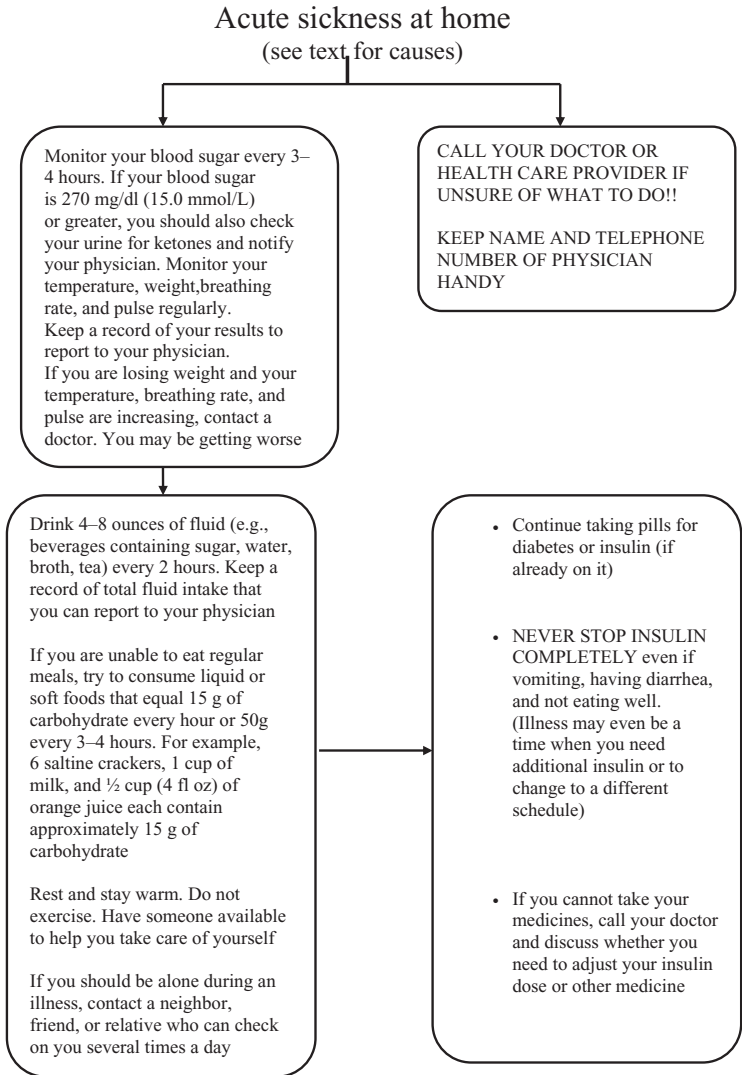


Figure 8.1 Proposed algorithm for the management of acute sickness at home.

stress that the acute illness has caused) rather than a reduction. This rule is more relevant to persons with T1DM. Additional doses of soluble insulin are likely to be needed and should be given as necessary to bring blood sugar down and suppress ketone production (e.g., rapid-acting insulin every 4 hours).

2. An increase in the frequency of capillary blood glucose measurements (at least every 3–4 hours) is recommended.
3. People with Type 1 diabetes (but also sometimes those with Type 2) should check their urine for ketones every 4–6 hours, depending also on blood glucose levels (most authors recommend ketone measurement when blood glucose levels exceed 270 mg/dl [15.0 mmol/L]). Some blood glucose meters allow testing for ketones in the blood as well (e.g., MediSense Xtra), and this is quite acceptable.¹¹ However, testing for ketones in the urine is a very sensitive test and there is no necessity to demonstrate ketone bodies in the blood. Self-monitoring of ketone bodies during hyperglycemia can provide important, complementary information on the metabolic state. Both methods for self-monitoring of ketone bodies at home are clinically reliable and there is no published evidence favoring one method with respect to DKA prevention.¹² It should be kept in mind, though, that ketones do not necessarily signify impending DKA because they can also be produced when people have not eaten anything for some time (starvation ketosis).¹³ Therefore, only the coexistence of high blood glucose levels and urine positive for ketones represents a true metabolic deterioration.
4. Ample intake of non-carbohydrate fluids (water) is advised (at least half a glass [100–150 ml] every hour). Food should be light.
5. Rest is advised. Exercise should be avoided.
6. Communication between the patient (family) and the treating physician is essential, so that appropriate instructions for coping with any special situation can be given at any time.
7. The goal should be to bring blood sugar down to acceptable levels (for example 80–180 mg/dl [4.4–10 mmol/L]) and to suppress urinary ketones to “small, trace, or negative” if they are positive.

Summary box

Insulin should never be omitted (in patients treated with insulin). Even when there is a feeding problem (nausea, vomiting), it is more likely that additional insulin will be needed (due to the stress that the acute illness has caused) rather than a reduction

In patients taking insulin—either basal only (\pm pills) or a more intensified regimen (insulin mixtures two or three times daily or a

basal-bolus regimen)—the “sick-day rules” should be taught and the patient should be provided with urine strips to test for ketones (e.g., Ketostix) and rapid-acting soluble insulin (human or insulin analog) along with their usual insulin and blood glucose testing kit.¹² Glucagon injection should also be available at home for family members to use in case of severe hypoglycemia. They should also have clear “contact criteria” and contact telephone numbers for their health care provider team (see “Patient advice” below).

For patients following an intensified insulin regimen (usually Type 1 diabetic patients) the insulin regimen is followed, basically, as it is, provided the patient is feeding normally. If needed, the doses of “prandial” and basal insulin are increased, based on frequent blood glucose measurements. Sometimes it may be necessary to administer rapid-acting insulin (or even better a rapid-acting insulin analog) in between meals. In this case, small doses are preferred. If the patient is unable to take food (due for example to nausea/vomiting), the dose of basal insulin is administered normally and, if needed, rapid-acting insulin is administered every 4–6 hours, or a rapid-acting analog every 3–4 hours.¹⁴ At the same time, intake of carbohydrates in the form of liquid or semi-solid food (i.e., juice, refreshments, soups, purée, etc.) is recommended. Insulin dose is empirically determined each time as 1/10th of the usual total daily dose when blood glucose is >150mg/dl (8.3 mmol/L), or as 1/5th of the total daily dose when blood glucose is >200mg/dl (11.1 mmol/L) or urine ketones are present. It is advisable to give specific numbers with examples and not just percentages. For instance, if the patient is using 40IU insulin in total, they should administer 4IU regular insulin if blood sugar is >150mg/dl (8.3 mmol/L) and 8IU when blood glucose is >200mg/dl (11.1 mmol/L).

Summary box

In patients taking insulin, the “sick-day rules” should be taught in advance and patients should be provided with urine strips to test for ketones (e.g., Ketostix) and rapid-acting soluble insulin (human or insulin analog) along with their usual insulin and blood glucose testing kit

When insulin is administered as a twice-a-day regimen (intermediate-acting or a mixture of rapid-acting [or analog]/

intermediate-acting, in the morning and evening), this scheme is initially preserved as it is if the patient is eating normally, additional rapid-acting (or rapid-acting analog) insulin may be administered in between, based on blood glucose measurements. If the patient is unable to eat (for example due to nausea/vomiting), a decrease in the insulin dose by 30–50% is recommended initially, as well as close monitoring of blood glucose levels, intake of carbohydrates in the form of liquid or semi-solid food, and possibly administration of rapid-acting (or analog) insulin.¹⁰ If the condition persists, it may be necessary to admit the patient to the hospital.

For patients taking pills, when diabetes is under good control (and theoretically there is adequate endogenous insulin reserve) there is usually not a great problem during an acute illness. There may be a mild rise in blood glucose during the period of acute illness, later returning to previous normal levels. If, however, blood glucose levels become high (usually >200 mg/dl [11.1 mmol/L]) or symptomatic, then a temporary period of insulin treatment with frequently repeated soluble insulin doses may be needed. People taking metformin should stop the drug during episodes of illness requiring hospital admission or confining them to bed (due to the potential risk of lactic acidosis).

Follow-up management/care

As people get better and blood sugars improve and/or ketonuria resolves, they should reduce their insulin back towards their usual dose (or, for patients who were previously on an oral antidiabetic regimen, stop insulin completely), guided by blood glucose measurements.

On the other hand, if the condition deteriorates, patients/family members should be prepared to go to the emergency room for urgent care. Criteria for transfer to the hospital are the following:

1. When poor glycemic control is accompanied by an alteration in the level of consciousness
2. Ketonuria or ketonemia are present and persist for more than 6 hours, despite the administration of insulin, carbohydrates, and fluids
3. Blood glucose levels >400 mg/dl (22.2 mmol/L) in >2 repeated measurements, despite the administration of rapid-acting insulin
4. Inability to receive hydration by mouth.

Summary box

If the condition deteriorates, patients/family members should be prepared to go to the emergency room for urgent care

Patient advice

Instructions to patients should be given beforehand, so that they are prepared to cope with an acute event. Written instructions are preferred. Some scientific organizations have written advice on their website (e.g., <http://www.diabetes.org.uk/>).

An example follows:

People with diabetes do not have more illness than others but if you do become unwell, it is likely that your blood glucose control will be upset. When you are sick, your body will release hormones that work to help your body fight against your illness, but they will also make your blood sugar levels rise. This means that your diabetes will be more difficult to control when you are sick. That is why it is so important to plan ahead and be prepared in case of illness.

Sickness can include: a cold, flu-like symptoms such as vomiting, diarrhea, sore throat, and infections such as ear, teeth, or bladder, or more serious illnesses such as pneumonia or a foot infection.

When to call your doctor

Minor illnesses in people with diabetes—especially children with Type 1 diabetes—can lead to very high blood sugar levels and possible emergencies. When children are sick, watch them closely for signs that they need immediate medical attention. Call your doctor or other emergency services if you or your child have:

- *Symptoms of diabetic ketoacidosis (DKA), such as abdominal pain, vomiting, rapid breathing, fruity-smelling breath, or severe drowsiness.*
- *Symptoms of dehydration, such as a dry mouth and very yellow or dark urine. Dehydration is particularly dangerous in children and elderly persons and may be caused by vomiting and diarrhea.*
- *A low blood sugar level (<70 mg/dl [3.9 mmol/L]) that continues.*

It may not be necessary to call your doctor every time you or your child with diabetes have a mild illness, such as a cold. But it is a good idea to call for advice when you are sick and:

- *Your blood sugar level is higher than 240 mg/dL (13.3 mmol/L) after taking the adjusted amount of insulin in your sick-day plan*
- *You take oral diabetes medicine and your blood sugar level is higher than 240 mg/dL (13.3 mmol/L) before meals and stays high for more than 24 hours*
- *You have more than 2+ or moderate ketones in your urine*
- *You still have a fever and are not feeling better after a few days*
- *You are vomiting or having diarrhea for more than 6 hours.*

When you are sick, write down the medicine(s) you have been taking and whether you have changed the dosage of your diabetes medicines based on your sick-day plan. Also note changes in your body temperature, weight, blood sugar, and urine ketone levels. Have this information handy when you talk to your doctor.

Plan ahead—steps to take during an illness

Some general sick-day guidelines:

- *Continue taking your pills for diabetes (if you have Type 2 diabetes) or insulin, even if you are vomiting and having trouble eating or drinking. Your blood sugar may continue to rise because of your illness. If you cannot take your medicines, call your doctor and discuss whether you need to adjust your insulin dose or other medicines. Metformin should be stopped if you are becoming dehydrated.*
- *Try to eat your normal types and amounts of food and to drink extra fluids, such as water, broth, carbonated drinks, and fruit juice. Encourage your child or loved one with diabetes to drink extra liquids to prevent dehydration.*
 - *If your blood sugar level is higher than 240 mg/dl (13.3 mmol/L), drink extra liquids that do not contain sugar, such as water or sugar-free soft drinks.*
 - *If you cannot eat the foods in your regular diet, drink extra liquids that contain sugar and salt, such as soup or milk. You may also try eating foods that are gentle on the stomach, such as crackers, gelatin, or apple sauce. Try to eat or drink 50 grams (g) of carbohydrate every 3 to 4 hours. For example, 6 saltine crackers, 1 cup of milk, and ½ cup (4 fl oz) of orange juice each contain approximately 15 g of carbohydrate.*
- *Check your blood sugar at least every 3 to 4 hours, or more often if it is rising quickly, even through the night. If your blood sugar level*

rises above 240 mg/dL (13.3 mmol/L) and your doctor has told you to take an extra insulin dose for high blood sugar levels, take the appropriate amount. If you take insulin and your doctor has not told you to take a specific amount of additional insulin, call him or her for advice.

- *If you take insulin, do a urine test for ketones every 4 to 6 hours, especially if your blood sugar is higher than 270 mg/dL (15.0 mmol/L). Call your doctor if you have more than 2+ or moderate ketones in your urine.*
- *Weigh yourself and check your temperature, breathing rate, and pulse frequently if your blood sugar is higher than 300 mg/dL (16.7 mmol/L). If you are losing weight and your temperature, breathing rate, and pulse are increasing, contact a doctor. You may be getting worse.*
- *Don't take any non-prescription medicines without talking with your doctor. Many non-prescription medicines affect your blood sugar level.*

Case studies

Case 8.1

A 28-year-old man with Type 1 diabetes for 12 years is under treatment with long-lasting insulin (e.g., insulin glargine) 26 IU at bedtime and a rapid-acting insulin analog (e.g., insulin lispro) three times a day before each meal (the dose determined depending on the carbohydrate content of the meal and the preprandial blood glucose level. The usual daily dose of insulin lispro is 22–24 IU). His glycemic control is quite good (recent HbA_{1c}: 6.7%). The patient calls his physician in the morning because he has been vomiting all night, has developed abdominal pains, and has a temperature of 38°C (100.4°F). His blood glucose level in the morning was 312 mg/dl (17.3 mmol/L). He was out at a party the previous night and was not able to hold anything down this morning, not even water.

The doctor initially asked the patient to check his urine for ketones with a special urine strip (that the patient had been instructed in the past to have at home) and call him back.

A few minutes later the patient informed the doctor that the urine test was positive for ketones (2+).

Based on the guidelines analyzed above, the doctor recommended the injection of 10IU of insulin lispro subcutaneously (20% of the total daily dose) and repeat blood glucose measurement and ketones in 2–3 hours. At the same time he asked the patient to try to sip tea slowly (at least one cup every 30–45 minutes), and to call again if urine ketones persisted after 6 hours (or earlier if they increased) or if blood glucose level was persistently higher than 300 mg/dl (16.7 mmol/L), despite the administration of insulin.

Two and a half hours later the patient had a blood glucose level of 230 mg/dl (12.8 mmol/L) and urine ketones had decreased to 1+. The tea had been relatively well tolerated, with only one episode of vomiting. Nausea had subsided but there had been two diarrheal bowel movements. The fever had subsided with antipyretics and the abdominal pain was much better.

The doctor advised another 10IU of insulin lispro subcutaneously and the tea to be continued.

Three hours later the patient felt much better. He had another diarrheal bowel movement, his blood glucose level was 170 mg/dl (9.4 mmol/L) and ketones were no longer detected in the urine.

He had a light meal (soup with chicken broth and some rice with a piece of toast and calculated the preprandial lispro dose as usual with an addition of 5IU (10% of total daily dose). In the afternoon he felt weak, but diarrhea and vomiting had ceased. Blood glucose level was 135 mg/dl (7.5 mmol/L) and no more insulin was administered. After his (light) dinner he returned to his regular schedule.

Case 8.2

A 72-year-old woman with Type 2 diabetes for 12 years is being treated with metformin (1000 mg twice a day) and glimepiride (4 mg per day). She lives with her 38-year-old daughter and her daughter's family at home. She also suffers from severe osteoarthritis of the hips, with limited ability to ambulate outside of the house. Her diabetic control is not very good (recent HbA_{1c}: 8.5%) but she has been refusing to start insulin, despite her physician's advice. Her usual blood glucose measurements range between 170 and 220 mg/dl [9.4–12.2 mmol/L].

She develops intense itching and burning on urination, together with increased thirst and urine production and has had very high blood glucose levels (>300 mg/dl [16.7 mmol/L]) for the last 2 days. She has had no fevers, chills, nausea, or vomiting. She took the initiative to increase her glimepiride dose to twice a day, but did not see much improvement and called her primary physician for advice.

The doctor advised her to send a urine specimen for urinalysis and culture at an outside laboratory and start antibiotics if there was evidence of an infection from the urinalysis. Regarding blood glucose control, he advised the patient to drink plenty of fluids (at least 2–3 liters per day), discontinue metformin, and start insulin, at least temporarily. He gave the patient the alternative of her or her daughter coming to the clinic for training on proper insulin injection technique or of her being admitted to the hospital for treatment and education.

Since the patient was not vomiting and was able to tolerate fluids and food, and since her ambulation was difficult, she opted for the first choice. Her daughter was trained in insulin administration technique and NPH and regular insulin were prescribed, to be used according to blood glucose levels (which she was advised to check frequently—at least 3 times a day before meals and occasionally 2 hours after a meal).

Urinalysis revealed increased WBC count and nitrite (+) urine. Antibiotics by mouth were started for 3 days for the lower urinary tract infection (UTI), to be changed according to urine culture and sensitivity results and clinical response. NPH insulin was started at an initial dose of 10 IU every night and regular insulin at 8 IU before meals. Metformin was temporarily discontinued.

Blood glucose levels next morning started to subside with treatment of the infection and NPH administration (down to 172 mg/dl [9.5 mmol/L]). Blood glucose levels for the rest of the day were monitored frequently (ranging between 150 and 200 mg/dl [8.3 – 11.1 mmol/L] preprandially and 180 and 250 mg/dl [10.0 – 13.9 mmol/L] postprandially) and the dose of regular insulin was adjusted accordingly.

By the second day the symptoms of the UTI had disappeared and the patient felt much better. She realized now that insulin administration was not a great nuisance and agreed to start it permanently. Metformin was restarted, glimepiride discontinued, and a twice-a-day regimen of a mixture of isophane/regular insulin (70/30 mixture) was started, the dose to be adjusted according to blood glucose measurements. The patient did not have to be admitted to the hospital.

Case 8.3

A 68-year-old man with Type 2 diabetes for 6 years is being treated with metformin (1000 mg twice a day) with adequate glucose control (recent HbA_{1c}: 6.9%). He checks his blood glucose at home 3–4 times per week, with usual levels around 130–160 mg/dl (7.2–8.9 mmol/L).

He has now (since the day before) developed symptoms of a common cold (fever, cough, sneezing, nasal congestion) and calls his physician for advice if anything needs to be changed in his diabetic regimen.

The doctor advises him to drink plenty of fluids and start checking his blood sugar more frequently (at least 3 times a day before meals and also sometimes 2 hours after a meal) and call him back if his levels consistently exceed 200 mg/dl (11.1 mmol/L). He also advises the patient to report to the clinic in case more severe symptoms arise (dyspnea, chest pains, increased thirst, and urination). He was advised to continue his metformin regimen as long as no signs of dehydration were present.

The patient's blood sugars ranged between 150 and 210 mg/dl (8.3–11.7 mmol/L) over the following 3 days and no change in his regimen was needed. He took antipyretics and over-the-counter antitussive cold medicine for his flu-like symptoms, which gradually improved. His blood sugar levels gradually returned to usual levels over the next 3 days.

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Multiple choice questions

Chapter 1

1. The pathogenesis of hyperglycemia in diabetic ketoacidosis includes all the following mechanisms except for:
 - a. Increased glycogenolysis in the liver
 - b. Increased gluconeogenesis in the kidneys
 - c. Increased serum glucagon
 - d. Increased gluconeogenesis in adipose tissue
 - e. Decreased glucose uptake from the muscles
2. Which of the following symptoms/signs are included in the clinical features of diabetic ketoacidosis?
 - a. Polyuria and weight loss
 - b. Tachypnea and tachycardia
 - c. Abdominal pain and vomiting
 - d. Cheyne–Stokes respiration
 - e. All of the above
 - f. a + b + c
3. A male with severe diabetic ketoacidosis is admitted to the hospital. Which of the following are his biochemical test results?
 - a. pH 7.21, PCO_2 27 mmHg, Ht 49%, glucose 490 mg/dl (27.2 mmol/L)
 - b. Ht 53%, HCO_3^- 15 mEq/L, K^+ 4.8 mEq/L, glucose 400 mg/dl (22.2 mmol/L)
 - c. PCO_2 17 mmHg, pH 6.95, K^+ 3.9, HCO_3^- 8 mEq/L, glucose 490 mg/dl (27.2 mmol/L)
 - d. pH 7.0, PO_2 109 mmHg, Na^+ 143 mEq/L, glucose 150 mg/dl (8.3 mmol/L)

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- e. Glucose 880mg/dl (48.9 mmol/L), white blood cell count 26,000/ μ l, Na^+ 159 mEq/L, HCO_3^- 28 mEq/L
4. A 35-year-old female with diabetic ketoacidosis is admitted to the hospital with the following profile: serum glucose 412mg/dl (22.9 mmol/L), pH 7.12, K^+ 4.4 mEq/L, Na^+ 141 mEq/L, and PO_4^{3-} 2.4 mEq/L (0.77 mmol/L). Which of the following is the appropriate initial treatment?
- a. Administration of hypotonic sodium chloride (0.45%) solution, potassium, and insulin
 - b. Administration of normal saline and insulin
 - c. Administration of normal saline, potassium, and insulin
 - d. Administration of normal saline, potassium, insulin, and bicarbonates
 - e. Administration of normal saline, insulin, and phosphate
5. Which of the following sentences about diabetic ketoacidosis is correct?
- a. Administration of glucose 5% solution is prohibited
 - b. Insulin can be administered subcutaneously in all cases of diabetic ketoacidosis
 - c. Blood glucose should be measured every 3 hours after initiation of treatment
 - d. All of the above
 - e. None of the above

Chapter 2

1. What is the first step in the management of diabetic ketoacidosis?
- a. To provide fluids intravenously
 - b. To provide insulin
 - c. To provide bicarbonate
 - d. To initiate insulin and fluids simultaneously
2. What is known about diabetic ketoacidosis in Type 2 diabetes in children and adolescents?
- a. Type 2 diabetes in childhood and adolescence never presents with diabetic ketoacidosis
 - b. Diabetic ketoacidosis is rarely the first manifestation of Type 2 diabetes in children and adolescents

- c. Diabetic ketoacidosis of Type 2 diabetes never necessitates insulin administration
 - d. Diabetic ketoacidosis is more frequent in Caucasian Type 2 diabetes patients than in Hispanic populations
- 3. What is correct concerning cerebral edema?
 - a. A patient with cerebral edema will present with tachycardia
 - b. Cerebral edema never supervenes before the initiation of fluid administration for the treatment of diabetic ketoacidosis
 - c. The treatment of cerebral edema is discontinuation of insulin administration
 - d. Cerebral edema is more frequent in younger patients with newly onset Type 1 diabetes
- 4. What is true concerning potassium in diabetic ketoacidosis?
 - a. Potassium replacement may not be necessary if its level is normal at initial management of DKA
 - b. Potassium deficiency may cause tall, peaked symmetrical T waves in the electrocardiogram
 - c. Potassium replacement is necessary during the whole time period of IV fluid administration
 - d. Potassium deficiency is the cause of hyponatremia observed at presentation of DKA
- 5. What is correct concerning fluid administration?
 - a. It is better to provide more fluids during the initial 12 hours of fluid administration
 - b. It is better to rehydrate evenly during the subsequent 48 hours of the management of DKA
 - c. Fluid administration should start simultaneously with insulin administration
 - d. Fluid administration is the main cause of cerebral edema
- 6. What is correct concerning the occurrence of DKA in a patient with known Type 1 diabetes? (There may be more than one correct answer)
 - a. DKA may supervene in an insulin pump user due to technical problems with the pump
 - b. DKA may supervene in a diabetic girl due to insulin omission in order to lose weight

- c. DKA may supervene during concurrent illness in a diabetic patient
- d. None of the above is correct

Chapter 3

1. A 67-year-old patient presents to the emergency room with uncontrolled diabetes. The following laboratory values are found: plasma glucose 920 mg/dl (51.1 mmol/L), serum Na^+ 148 mEq/L, serum K^+ 3.9 mEq/L, BUN 68 mg/dl (24.3 mmol/L). The effective serum osmolality is:

- a. 355.5
- b. 347.1
- c. 371.4
- d. 379.8

2. A 72-year-old diabetic patient with end-stage renal disease on hemodialysis comes to the emergency room with fever (up to 38.2°C [100.8°F]) of 5 days duration. He is found to have pneumonia of his right lung, marked hyperglycemia (plasma glucose 1080 mg/dl [60.0 mmol/L]), and low serum Na^+ 123 mEq/L, K^+ 3.9 mEq/L, arterial blood pH 7.31. Which of the following is true?

- a. Based on these lab values, his mental status is expected to be normal
- b. The patient is in a severe hyperosmolar state
- c. His low serum Na^+ level is due to osmotic glucose-induced diuresis
- d. He most likely has diabetic ketoacidosis

3. A 77-year-old diabetic patient is being treated for HHS with continuous IV insulin infusion of 7 IU/h and 0.9% normal saline at a rate of 250 ml/h. A few hours later he is found to have a plasma glucose level of 58 mg/dl (3.2 mmol/L). He is started on 5% dextrose at a rate of 250 ml/h. Which of the following is an appropriate next response?

- a. Decrease the insulin infusion rate to 4 IU/h
- b. Increase the insulin infusion rate to 10 IU/h to compensate for the intravenous glucose given
- c. Stop the insulin infusion and start subcutaneous insulin
- d. Continue the IV insulin infusion at 7 IU/h

4. Which of the following statements is false?
 - a. Hyperosmolar hyperglycemic state (HHS) and diabetic ketoacidosis (DKA) can overlap in some patients
 - b. Abdominal pain is a common feature of HHS
 - c. Severe dehydration is common in HHS
 - d. Despite total body K^+ deficit, serum K^+ is usually normal or elevated at presentation in HHS

5. A 78-year-old woman with history of Type 2 diabetes for 10 years is hospitalized with obtundation after suffering a stroke. On presentation she is hypotensive (BP 80/50 mmHg) and tachycardic (pulse rate 122 bpm), with serum Na^+ 141 mEq/L and plasma glucose 1245 mg/dl (69.1 mmol/L). The serum bicarbonate is normal and urinary ketones are absent. Which of the following is the most appropriate therapy for this patient?
 - a. Intravenous half-normal saline and insulin infusion simultaneously
 - b. Intravenous normal saline followed by intravenous insulin infusion
 - c. Intravenous half-normal saline followed by intravenous insulin infusion
 - d. Intravenous insulin infusion followed by normal saline

6. Which of the following statements is false?
 - a. Altered mental status is the most common reason patients with HHS are brought to the hospital
 - b. In a comatose diabetic patient with an effective serum osmolality <320 mOsm/kg, another cause of the impaired mental state should be sought
 - c. Patients with HHS usually have an increased anion gap metabolic acidosis
 - d. Insulin therapy lowers the K^+ concentration and may cause severe hypokalemia

7. Which of the following statements is true?
 - a. The mortality rate in HHS is around 1%
 - b. Myocardial infarction can be a precipitating event for HHS to develop
 - c. Patients with HHS usually have normal renal function
 - d. Hyperglycemia in HHS is usually due to excessive oral carbohydrate intake

Chapter 4

1. The first counter-regulatory mechanism to be elicited against hypoglycemia in normal persons is:

- a.** Epinephrine release
- b.** Glucagon release
- c.** Inhibition of insulin release
- d.** Growth hormone release
- e.** Cortisol release

2. All of the following are true for hypoglycemia-associated autonomic failure (HAAF) except:

- a.** HAAF is usually observed after recent antecedent iatrogenic hypoglycemia
- b.** HAAF is observed only in patients with autonomic neuropathy
- c.** HAAF can be related to sleep or exercise
- d.** HAAF is a predisposing factor for severe hypoglycemia
- e.** HAAF may be improved by meticulous avoidance of iatrogenic hypoglycemia

3. Which of the following is a predisposing factor for hypoglycemia in insulin-treated patients?

- a.** Renal failure
- b.** Older age
- c.** Hypoglycemia unawareness
- d.** Alcohol ingestion
- e.** Adrenal insufficiency
- f.** All of the above

4. Management of a hypoglycemic episode includes (more than one answer possible):

- a.** The administration of glucagon in every patient with severe hypoglycemia
- b.** The administration of oral carbohydrates if the patient is able to swallow food
- c.** Hospitalization if plasma blood glucose at admission is below 40 mg/dl (2.2 mmol/L)
- d.** The administration of IV glucose if the patient is admitted unconscious to the emergency department

- e. The administration of glucocorticoids to every patient presenting with coma
5. A patient with severe hypoglycemia should be hospitalized in case of (more than one answer possible):
- a. An initial plasma glucose value <50 mg/dl (2.8 mmol/L)
 - b. An initial plasma glucose value <30 mg/dl (1.7 mmol/L)
 - c. Presentation with coma
 - d. Persistent nausea and vomiting
 - e. Recurrence of hypoglycemia 2 hours after presentation despite IV glucose infusion

Chapter 5

1. Which of the following sentences is correct?
- a. Glibenclamide (glyburide) causes hypoglycemia less often than glimepiride
 - b. Meglitinides rarely cause severe hypoglycemia
 - c. Sulfonylureas cause hypoglycemia more often than insulin
 - d. Monotherapy with dipeptidyl-peptidase IV inhibitors is a common cause of hypoglycemia
2. Which of the following sentences is wrong?
- a. Second generation sulfonylureas are metabolized mainly in the kidneys
 - b. Meglitinides are metabolized in liver
 - c. Gliclazide is primarily metabolized in liver
 - d. The duration of action of meglitinides is 2–6 hours
3. Risk factors for drug-induced hypoglycemia are the following, except for:
- a. Advancing age
 - b. Reduced food intake
 - c. Use of glucagon-like peptide 1 agonists in combination with metformin
 - d. Renal impairment

4. In a patient treated with glimepiride you have to prescribe ciprofloxacin for a genitourinary tract infection. Which of the following is correct?

- a. There is no drug interaction between ciprofloxacin and glimepiride
- b. You will prescribe a half dose of ciprofloxacin to avoid potential hypoglycemia
- c. You will treat the patient with another antimicrobial agent with doubtful activity against the pathogen
- d. You will prescribe ciprofloxacin and you will advise the patient to perform frequent self-monitoring of blood glucose to prevent hypoglycemia

5. A patient with Type 2 diabetes is being treated with the combination of repaglinide and metformin. His triglyceride levels are high despite good diabetes control. Which of the following lipid-lowering medications has the potential for known drug interactions with repaglinide and hypoglycemia?

- a. Fenofibrate
- b. Gemfibrozil
- c. Omega-3 fatty acids
- d. Clofibrate

6. Which of the following sentences is/are correct?

- a. Counter-regulation in hypoglycemia in subjects with Type 2 diabetes treated with sulfonylureas occurs at higher blood glucose levels than in people with Type 1 diabetes
- b. Advancing age is associated with a blunted counter-regulation response to hypoglycemia
- c. Elderly people may not have enough time to take action for the correction of hypoglycemia because symptoms occur late after the onset of neuroglycopenia
- d. All the above are correct

7. All the following statements about people with Type 2 diabetes are correct, except for:

- a. Symptoms of hypoglycemia may be different in elderly people compared to younger people
- b. Hemiplegia may be a manifestation of hypoglycemia

- c. Concomitant medications may mask hypoglycemic symptoms
 - d. Warm skin is the rule in people with hypoglycemia
8. A patient with Type 2 diabetes treated with glimepiride was taken to the emergency room because of disorientation and slurred speech. His blood glucose is 50mg/dl (2.8mmol/L). How will you manage the patient?
- a. You will correct hypoglycemia with a bolus injection of 50ml glucose solution 35% and you will re-check his blood glucose after 15 minutes
 - b. You will correct hypoglycemia with a bolus injection of 50ml glucose solution 35% and you will suggest the patient has a carbohydrate-rich meal
 - c. You will correct hypoglycemia with a bolus injection of 50ml glucose solution 35% immediately followed by infusion of glucose 10% solution and you will admit the patient to the hospital for 24–72 hours
 - d. You will correct hypoglycemia with a bolus injection of 50ml glucose solution 35% followed by infusion of glucose 10% solution and you will discharge him after 6 hours if the blood glucose over this time is in the normal range

Chapter 6

1. Which of the following sentences is correct?
- a. Diabetes per se is a very rare cause of lactic acidosis
 - b. Metformin is the commonest cause of lactic acidosis in patients with Type 2 diabetes mellitus
 - c. In patients with diabetic ketoacidosis blood lactate levels are usually high
 - d. Metformin-associated lactic acidosis is usually of Type A
2. Which of the following sentences is correct?
- a. The normal blood lactate levels are usually less than 3.5mmol/L
 - b. Lactate is an acid that causes lactic acidosis

- c. Acidosis during the anaerobic metabolism of glucose is the result of ATP hydrolysis and excess release of lactate and hydrogen ions into the blood stream
 - d. Symptoms and signs of lactic acidosis differ from those of metabolic acidosis from other causes
- 3. A 74-year old man with Type 2 diabetes diagnosed 2 years before attended the diabetes outpatient clinic. His diabetes control was good in the past with HbA_{1c} 6.8%; however, he noticed in the last 4 months that his average blood glucose levels were 160mg/dl (8.9mmol/L) in the morning and 220mg/dl (12.2mmol/L) in the afternoon. His recent HbA_{1c} was 7.6% and you consider prescribing metformin monotherapy. His serum creatinine is 1.4mg/dl (123.8 μ mol/L). Which of the following is correct?
 - a. Serum creatinine level is a safe way to administer metformin
 - b. Calculation of GFR using the MDRD formula is recommended to avoid metformin-associated lactic acidosis
 - c. Metformin is contraindicated in elderly patients
 - d. You will ask for determination of GFR in a 24-h urine collection before prescribing metformin
- 4. Diagnosis of lactic acidosis is made when:
 - a. Blood lactate levels are >2.5 mmol/L and pH is normal
 - b. Blood lactate levels are >5 mmol/L and there is a non-anion gap metabolic acidosis
 - c. Blood lactate levels are >5 mmol/L and pH is <7.35
 - d. Blood lactate levels are >5 mmol/L and pH is <7.0
- 5. Which of the following sentences is correct?
 - a. Metformin is contraindicated in all patients with a serum creatinine >1.4mg/dl (123.8 μ mol/L)
 - b. Metformin can be used safely in patients hospitalized for heart failure
 - c. Metformin is contraindicated in patients with chronic stable angina
 - d. Metformin is contraindicated in patients who have GFR <30ml/min per 1.73m²

6. A man with a history of gastric bypass surgery for morbid obesity presented to the emergency room with rapid and deep breathing, nausea, and altered mental status after treatment with doxycycline for acute bronchitis. His arterial blood pH was 7.02 and arterial blood lactate levels 1.23 mmol/L. What is your diagnosis?

- a. Acute respiratory failure
- b. D-lactic acidosis
- c. Hepatic encephalopathy
- d. Central nervous system infection

Chapter 7

1. All of the following sentences regarding in-hospital glycemic control are correct, except:

- a. According to current (2010) guidelines, glycemic control for critically ill ICU patients should generally aim at blood glucose levels between 80 and 110 mg/dl (4.4–6.1 mmol/L)
- b. Several epidemiological studies have shown that, in the hospital setting, there is a positive association between hyperglycemia and mortality
- c. Very strict glycemic control in the ICU has been associated with increased mortality in the largest multicenter study conducted to test this association
- d. Clinical trials examining the association between glycemic control and patient outcomes have been performed exclusively in the ICU setting
- e. In non-critically ill patients, preprandial blood glucose control should generally aim at levels <140 mg/dl (7.8 mmol/L)

2. In which of the following situations is intravenous insulin infusion the preferred route for the treatment of hyperglycemia?

- a. Myocardial infarction
- b. Heart operation
- c. Renal failure
- d. Diabetic ketoacidosis
- e. Shock

3. Which of the following sentence(s) is/are correct regarding treatment of hyperglycemia in hospitalized, non-critically ill patients?

- a.** In-hospital use of sulfonylureas is contraindicated
- b.** Basal insulin should not be administered when insulin therapy is implemented in insulin-naïve patients
- c.** Subcutaneous insulin should not be administered in case of shock
- d.** Sliding scales depicting short-acting insulin administration should be individualized
- e.** Portable glucose meters should not be used in order to adjust insulin dose

4. Which of the following sentence(s) is/are correct regarding peri-operative treatment of hyperglycemia?

- a.** All diabetic patients undergoing major surgery should start insulin treatment one week before the operation
- b.** Patients with Type 1 diabetes and poor glycemic control should be admitted to the hospital 24–48 hours before any type of surgery
- c.** Intravenous insulin infusion is the preferred way to control blood glucose intraoperatively
- d.** Glucose–insulin infusion is the preoperative treatment of choice for all diabetic patients undergoing minor surgery

Chapter 8

1. Which of the following sentences is true?

- a.** A patient on insulin who starts vomiting should definitely stop insulin administration because of the risk of hypoglycemia
- b.** If blood sugar levels exceed 270 mg/dl (15.0 mmol/L) patients should check their urine for ketones
- c.** Patients on metformin should never stop their medicine during an acute illness
- d.** Patients with impending DKA can usually manage their condition at home

2. A 28-year-old man with Type 1 diabetes develops symptoms of an upper respiratory tract infection, with fever and cough. His usual insulin regimen consists of insulin detemir 8IU before breakfast and 10IU at bedtime and insulin aspart 6–10IU before each meal, based on blood glucose measurements and carbohydrate counting of meals. His latest blood glucose measurements are in the range of 250–280mg/dl (13.9–15.6mmol/L). Which of the following is false regarding his treatment options?

- a.** He should continue his insulin regimen and give 5–6 extra units of insulin aspart before meals
- b.** He should double insulin detemir to cope for the increased demands due to the infection
- c.** He should drink plenty of non-carbohydrate containing fluids (at least 3 liters per day)
- d.** He should check his blood sugar levels every 2–3 hours together with ketone bodies in the urine

3. Which of the following is false?

- a.** When poor glycemic control is accompanied by an alteration in the level of consciousness the patient should be transferred to the hospital
- b.** People with diabetes are more prone to all types of infections compared to people without diabetes
- c.** When urine ketones are positive, it may signify glycemic deterioration
- d.** Symptoms of dehydration are a dry mouth and very yellow or dark urine

4. A 17-year-old boy whose 22-year-old brother has Type 1 diabetes starts having vomiting, abdominal pain, deep rapid breathing, and fruity breath in the middle of the night. Which of the following should be done?

- a.** He should stop eating and wait until dawn to go to the doctor
- b.** He should take antacids and non-steroidal anti-inflammatory pills
- c.** The family should check a blood glucose level at home to diagnose possible initial manifestation of Type 1 diabetes with impending DKA
- d.** Food poisoning is the most likely cause and should subside without any action being taken

5. Which of the following statements is false?
- a. A urine test for glucose is reliable to monitor the progress of diabetic control during an acute illness
 - b. Diabetic patients should discuss with their physician beforehand what to do if an acute illness occurs
 - c. Diabetic people who cannot tolerate any food or fluids because of repeated vomiting should go to the hospital for IV fluid hydration
 - d. If ketonuria is present and persists for more than 6 hours, despite the administration of insulin, carbohydrates, and fluids, diabetic persons should go to the hospital

Answers to multiple choice questions

Chapter 1

1. d
2. f
3. c
4. c
5. e

Chapter 2

1. a
2. b
3. d
4. c
5. b
6. a, b, c

Chapter 3

1. b
2. a
3. c
4. b
5. b
6. c
7. b

Chapter 4

1. c
2. b
3. f
4. b, d
5. d, e

Chapter 5

1. b
2. a
3. c
4. d
5. b
6. d
7. d
8. c

Chapter 6

1. a
2. c
3. b
4. c
5. d
6. b

Chapter 7

1. a
2. a, b, d, e
3. c, d
4. b, c

Chapter 8

1. b
2. b
3. b
4. c
5. a

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